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# PULMONARY ARTERIOVENOUS FISTULAE[1]

By B. T. Le ROUX

(From the Departments of Surgery, University of Edinburgh)

With Plates 1 to 4

Congenital fistulous communications between branches of pulmonary arteries and veins within the lung are vascular hamartomata. The term hamartoma was introduced by Albrecht (1904), and is applied to developmental tumour-like malformations in which the normal components of an organ are represented abnormally. The abnormality may be in the quantity of the components, in their arrangement, in the degree of their differentiation, or in all three (Ronald, 1954). During development the opportunity is presented for the persistence of abnormal communications between arteries and veins, since these arise from a common capillary plexus. Pulmonary arteriovenous fistulae probably result from the incomplete fusion of venous and arterial septa, or from the disintegration of hypoplastic septa in the face of normal or abnormal stresses. The lesion has been defined as a congenital haemangiomatous malformation of the pulmonary vascular bed (Steinberg and McClenahan, 1955). The essential anatomy is that of a vascular shunt which permits of venous blood by-passing the pulmonary capillaries. It is often associated with telangiectasis in other areas. A family history is not uncommon, and there is a well recognized hereditary tendency (Goldman, 1948; Moyer and Ackerman, 1948; Yater, Finnegan, and Giffin, 1949; Seaman and Goldman, 1952; Alexander and Harrington, 1955). The lesion is almost certainly a manifestation of multiple hereditary haemorrhagic telangiectasis, or Rendu-Osler-Weber disease. Uniformity in nomenclature has not been achieved. The terms cavernous haemangioma, congenital arteriovenous varix, multiple pulmonary haemangiomata, pulmonary arteriovenous aneurysm, and pulmonary arteriovenous fistulae, are all used synonymously. The last seems the proper designation, since the lesion is a fistula, with afferent arterial and efferent venous connexions, and not an aneurysm.

Six examples of pulmonary arteriovenous fistula are described below, and the natural history of the disease is discussed.

*Case 1.* A 29-year-old housewife was referred for investigation of a pulmonary opacity and cyanosis. She remembered that when she was at school she had been less able than her fellows to cope with normal activities. She was made more easily breathless by exertion, and she vaguely remembered being told that she

[1] Received February 1, 1958.

was sometimes blue in the face. During the five years preceding her admission to hospital she had had three pregnancies, and had been cyanotic throughout them. She was certain that her fingers had become progressively more bulbous at the tips. Between pregnancies she had been unaware of cyanosis. She volunteered, however, that for about six or seven years she had frequently had to change the shade of her cosmetics to suit her deepening colour. Her only respiratory symptom was dyspnoea; she had frequently to rest during a normal day's housework. There was no personal or family history of epistaxis, haemoptysis, or other haemorrhage. On examination she was deeply cyanotic, her fingers were clubbed, and there were no cutaneous or mucosal telangiectases. There was a continuous murmur, loudest in systole, and on expiration best heard in the right anterior axillary line. The heart was clinically, radiographically, and electrocardiographically normal. Radiographs of the chest showed a lobulated opacity in the right lower lobe, connected to the pulmonary hilum by large vascular shadows (Plate 1, Figs. 1 and 2). Behind the X-ray screen the opacity pulsated fairly vigorously, and increased in size with the Müller manœuvre and diminished in size with the Valsalva manœuvre. The bronchi were normal bronchoscopically. A clinical diagnosis of pulmonary arteriovenous fistula was made.

Arterial oxygen saturation was 79·4 per cent., haemoglobin 110 per cent., and the volume of packed cells 58 per cent. Cardiac catheterization demonstrated a high cardiac output of eight litres per minute, of which it was estimated that four litres were passing through the fistula. An angiogram was made, four separate injections being given, one for each lung in the anterior and lateral views. The arteriovenous fistula in the right lower lobe was outlined at half a second (Plate 1, Fig. 3). Some venous filling was seen at one second, and the vein was best outlined at one and a half seconds (Plate 1, Fig. 4). Contrast medium was still in the fistula at the end of the series at five and a half seconds. No other fistulae were outlined.

A standard right thoracotomy was made through the bed of the resected seventh rib. There were no pleural adhesions, and no effusion. Over the anterior and lateral basal segments there was a thickened plaque of pearly-white pleura about 4 cm. square. At the edge of this square there was an area, about 1·5 cm. in diameter, over which the pleura was abnormally thin, purple in colour, and through which blood could be seen swirling. The whole area pulsated vigorously. The rest of the lung was normal. The artery to the lower lobe was exposed in the oblique fissure; it was estimated to be about twice the usual size, and was abnormally thin. The lower vein was 3 cm. in diameter. Some eight or 10 small vessels traversed the oblique fissure, and were much larger than any vessel normally seen in this situation. All of them required ligation. Lower lobectomy was undertaken. Convalescence from the operation was uneventful. A rubber cast was made of the fistula and its vascular connexions (Plate 2, Fig. 5).

Cyanosis had disappeared by the time the patient returned to the ward from the operating theatre. Three weeks after operation her haemoglobin was 100 per cent., volume of packed cells 46 per cent., and arterial oxygen saturation 93 per cent. Within a month of her return home exercise tolerance had greatly improved. Five months after operation she had gained a stone in weight, and the arterial oxygen saturation was 96 per cent. Her fingers had reverted so nearly to normal that she could wear a thimble she had not been able to wear since she had been at school. Her only complaint was that she had again found it necessary to buy a new shade of cosmetic.

*Case 2.* A 50-year-old paper-maker developed bilateral renal calculi during

prolonged immobilization for a fractured femur. Renal damage was severe, and right nephrectomy and left nephrolithotomy were carried out. X-rays made during pyelography included part of the right lower chest, and showed a spherical opacity in the right posterior basal segment. Further X-rays and tomograms (Plate 2, Figs. 7 and 8) clearly demonstrated the opacity. He had no respiratory complaints. He was cyanotic, and his fingers were clubbed. There were telangiectases on the mucosa of the lips, tongue, cheeks, and palate. A brother, an uncle, and the father of the patient had similar mucosal lesions, which bled frequently. A murmur was heard in systole at the right base posteriorly. On screening, the opacity moved with the diaphragm, but pulmonary translucency separated it from the diaphragm in full inspiration. Alterations in the size of the opacity were seen with the Müller and Valsalva manœuvres. The bronchi were normal bronchoscopically, and the heart was normal clinically, radiographically, and electrocardiographically. Arterial oxygen saturation was 86 per cent. When he had breathed pure oxygen for five minutes this figure rose to 88·5 per cent., so that there was a significant degree of arterial oxygen unsaturation not corrected by breathing oxygen at a high flow rate. The haemoglobin was 115 per cent., and the volume of packed cells was 53 per cent.

Catheterization and angiography were undertaken. A No. 9 aortographic catheter was passed into the pulmonary circulation under local anaesthesia. The pulmonary arterial pressure was within normal limits (22/5 mm. Hg) as was the pulmonary wedge pressure (10/6 mm. Hg in expiration and 4/1 mm. Hg in inspiration). Under pentothal anaesthesia a pressure injection of 30 ml. of contrast medium was made into the pulmonary artery. The patient was not clinically disturbed, but the electrocardiogram showed ventricular anarchy for 10 beats, and the catheter whipped back into the infundibulum of the right ventricle. The electrocardiogram showed right bundle branch block for 24 hours, and was thereafter normal. The main right and left pulmonary arteries were filled at half a second. The opacity was well-outlined at two seconds (Plate 2, Fig. 6). Most of the draining vein was filled at three and a half seconds, but the vascular anomaly was still outlined at six seconds. Small additional fistulae were shown in the upper part of the right lung and in the left lower lobe. Because of the patient's poor renal reserve he was not submitted to resection of the fistulae.

*Case 3.* A 57-year-old housewife was referred for investigation of dyspnoea. She gave a history of a small haemoptysis two years previously, and of frequent nose bleeding. She, her sister, and her mother, had telangiectases on their lips, and she complained that these bled whenever she ate hard foods such as toast. Two brothers, four other sisters, and her twin daughters, all had frequent epistaxis. She was slightly cyanotic. There were further telangiectases on the tongue and hard palate, and on the fingers, which were clubbed. Her blood-pressure was 185/110 mm. Hg. She showed clinical and radiographic evidence of mitral stenosis, with a normal electrocardiogram, and without previous history of rheumatic fever. There was no mitral systolic murmur. A systolic murmur was heard in the fifth and sixth right intercostal spaces, medial to the angle of the scapula. The murmur waxed and waned in intensity with the phases of respiration, became continuous after cessation of respiration for 20 seconds in expiration, and remained continuous for 10 or 12 cardiac cycles after resumption of respiration. X-rays showed a lobulated opacity in the right lower lobe, with vascular shadows connecting it to the pulmonary hilum (Plate 3, Figs. 9 and 10). Tomograms demonstrated both the lobulation and the hilar connexions more clearly (Plate 3, Fig. 11). The bronchi appeared

normal on bronchoscopy. The haemoglobin was 100 per cent., volume of packed cells 49 per cent., and arterial oxygen saturation 87·7 per cent. After she had breathed pure oxygen for five minutes the arterial saturation was 96 per cent. This normal figure was an unexpected finding, not apparently related to technical error.

Cardiac catheterization showed slight pulmonary hypertension: the pulmonary arterial pressure was 44/20 to 60/25 mm. Hg, with a mean pressure of 35 mm. Hg. Angiocardiography demonstrated two arteriovenous fistulae in the right lower lobe (Plate 3, Fig. 12), the largest 3·5 cm. in diameter. Draining veins were filled at two seconds. There was a small third fistula in the left lower lobe. Resection of the fistulae was recommended, but the patient declined operation. She was well, without any increase in her dyspnoea, two years later. (See *Addendum*.)

*Case 4.* A 30-year-old housewife complained of dyspnoea on exertion, of increasing severity, for two years, and orthopnoea for six months. Her face, lips, hands, and feet had been blue for a year. She gave no history of rheumatism. She was cyanotic, and her fingers were clubbed; there were continuous murmurs in the right and left axillae, and the classical clinical, radiographic, and electrocardiographic signs of severe mitral stenosis. There were large lobulated vascular shadows in the anterior segments of both lower lobes. The haemoglobin was 120 per cent., and the volume of packed cells was 58 per cent. Arterial oxygen saturation was not estimated, and an angiogram was not made. With the diagnosis of mitral stenosis and bilateral pulmonary arteriovenous fistulae, she was submitted to left thoracotomy as a first step. The upper lobe was densely adherent at the apex, and contained some hard nodules assumed to be tuberculous. At the periphery of the left anterior basal segment there was a soft blue prominence, 2 cm. in diameter, which emptied easily on pressure. No other pulmonary abnormality was found. The mitral valve admitted the tip of the index finger, and both commissures were easily split with the finger; thereafter there was a faint regurgitant jet. The arteriovenous fistula in the anterior segment was resected, including a wedge of lung, between clamps. The contributing vessels were all about 0·5 cm. in diameter.

Four months later she was readmitted with a view to resection of the right pulmonary lesion. She said that she had been greatly improved by the first operation for about three months, had become very much less blue, and was easily able to do her housework, but that she had felt less well for a month, and she thought her colour had deepened a little. She had gained a stone in weight, and was so impressed with her improvement that she had to be persuaded to submit to a second operation. The tomograms made of the left fistula before the first operation, and the radiograph of the chest made before the second operation, are shown in Plate 4 (Figs. 13 and 14). At right thoracotomy there was a large arteriovenous fistula in the anterior basal segment, supplied by the medial and anterior basal segmental arteries. These vessels were tied and divided, as were the medial and anterior basal veins, which were much larger than normal. The afferent and efferent vascular communications and the fistula were stripped out of the basal segment without any appreciable loss of pulmonary tissue. Three small additional fistulae in the lateral and posterior basal segments were similarly dissected without loss of lung. Two 1 mm.-sized purple spots on the upper lobe were not resected.

Three months after the second operation the haemoglobin was 100 per cent., and volume of packed cells 46 per cent. She was well, not dyspnoeic, and managing her household duties easily. Two months later she began to experi-

ence rapidly increasing dyspnoea. She was admitted to a medical ward elsewhere, was found to be very breathless, and showed clinical features interpreted as those of gross pulmonary hypertension. She died after four weeks in hospital. Histologically the lungs showed pulmonary arteriolar necrosis. No additional arteriovenous fistulae were reported in the lungs.

*Case 5.* A 46-year-old brewery worker complained of increasing dyspnoea for five years, and haemoptysis for three months. Seventeen years earlier he was examined in the army after a syncopal episode, and was told that he had valvular heart disease; he was thereafter discharged from the army. He had not suffered from rheumatic fever. Clinically, radiographically, and electrocardiographically there were all the evidences of severe mitral stenosis. His fingers were clubbed. There were no other clinical abnormalities. The haemoglobin was 90 per cent., volume of packed cells 43 per cent., and arterial oxygen saturation 96 per cent. The bronchi were normal. There were no murmurs apart from those of mitral disease. There was a lobulated opacity in the right lower lobe, connected to the pulmonary hilum by vascular shadows. Tomograms showed this opacity to be a typical pulmonary arteriovenous fistula. Angiocardiograms were not made. As a first measure he was submitted to mitral valvulotomy through a left thoractomy. The left lung was normal. The stenosis was severe, and complete anterior and posterior commissurotomy was achieved with a transventricular expanding dilator. Six months later his exercise tolerance was greatly improved. Angiocardiography is planned for the future, and the need for resection of his right pulmonary arteriovenous fistula will then be considered.

*Case 6.* A 43-year-old schoolmistress complained of increasing dyspnoea for 10 years, and attacks of asthma for two years, these attacks being precipitated by exertion. As a child she had been prevented from taking part in normal physical activity, for reasons not made clear to her. From the time she started teaching she had been able to referee hockey matches without becoming dyspnoeic. She gave a history of frequent epistaxes as a girl, and epistaxes had often occurred in all the members of her family. Her fingers were normal, and she was not cyanotic. There were numerous telangiectases on the lips and tongue. In the left anterior axillary line a systolic murmur was heard. Phonocardiograms demonstrated a diastolic element as well. The murmur disappeared with the Valsalva manœuvre, and was augmented by the Müller manœuvre. Plain films and tomograms showed two small opacities in the left anterior basal segment, connected to the pulmonary hilum by large vascular shadows. Angiocardiography showed that they were pulmonary arteriovenous fistulae; no further fistulae were demonstrated. The haemoglobin was 80 per cent., volume of packed cells 39 per cent., and arterial oxygen saturation 96 per cent. The bronchi were normal, and the opacities did not change on screening, but they were small and difficult to see. The maximum breathing capacity was 39 litres per minute, compared with a predicted normal value for the patient of 86 litres per minute. Other respiratory function tests showed her to have emphysema. An attack of bronchospasm was induced by the estimation of her maximum breathing capacity.

The fistulae in this patient were small, and she did not have an important shunt. Her symptoms were considered to be due to emphysema rather than to the pulmonary arteriovenous fistulae. Thoracotomy alone would probably have reduced her exercise tolerance, even if the fistulae could have been resected without the sacrifice of any pulmonary tissue. It was therefore decided that

she should not be submitted to resection of the fistulae. Her condition remains unchanged a year later, without any alteration in her maximum breathing capacity.

The clinical data from these six cases are summarized in Table I.

TABLE I

*Clinical Data*

| | *Case 1* | *Case 2* | *Case 3* | *Case 4* | *Case 5* | *Case 6* |
|---|---|---|---|---|---|---|
| Age (years) | 29 | 50 | 57 | 30 | 46 | 43 |
| Sex | F | M | F | F | M | F |
| Dyspnoea | + | − | + | + | + | + |
| Cyanosis | + | + | + | + | − | − |
| Clubbing | + | + | + | + | + | − |
| Murmur | + | + | + | + | − | + |
| Normal heart | + | + | − | − | − | + |
| Mitral stenosis | − | − | + | + | + | − |
| Haemoglobin (%) | 110 | 115 | 100 | 120 | 90 | 80 |
| Packed cell volume (%) | 58 | 53 | 49 | 58 | 43 | 39 |
| Arterial oxygen saturation (%) | 79·4 | 86 | 87·7 | .. | 96 | 96 |
| X-ray opacity | + | + | + | + | + | + |
| Number of fistulae | 1 | 3 | 3 | 5 | 1 | 2 |
| Other telangiectases | − | + | + | − | − | + |
| Family history of telangiectasis | − | + | + | − | − | + |

*History*

The first systemic arteriovenous fistulae were recorded by William Hunter in 1762. He described two cases following injury to the brachial vessels during blood-letting. In 1897 Churton reported an autopsy finding of multiple haemangiomatous lesions in the lungs. These he called aneurysms of the pulmonary artery, but from his description they were almost certainly pulmonary arteriovenous fistulae. In 1917 Wilkens described the autopsy findings in a woman who had died from massive pleural haemorrhage, and in whom an unusual bruit had been detected. The three lesions which he described in the lungs, from one of which the haemorrhage had occurred, were typical pulmonary arteriovenous fistulae. In 1938 Rodes described and named three pulmonary arteriovenous fistulae in the lungs of a disabled polycythaemic patient, who died from pulmonary haemorrhage. A retrospective and accurate interpretation of the relationship between the clinical picture and the autopsy findings was made. The first ante-mortem diagnosis on clinical and radiographic evidence was made by Smith and Horton in 1939. In 1942 Hepburn and Dauphinee reported an example of the lesion diagnosed clinically, and treated surgically by pneumonectomy. The operation was undertaken by Shenstone (1942), who used the tourniquet technique. The patient later developed additional fistulae in the remaining lung, which were successfully resected (Adams, Thornton, and Eichelberger, 1944; Charbon, Adams, and Carlson, 1952). The history of pulmonary arteriovenous fistula, and of the closely related condition of hereditary haemorrhagic telangiectasis, is reviewed in detail by Stringer, Stanley, Bates, and Summers (1955).

### *Morbid Anatomy*

The existence of normal channels of greater diameter than capillaries, connecting branches of pulmonary arteries and veins, has long been suspected on the basis of gas analyses, and by the passage through the lungs of large particles such as clumps of tumour cells and certain parasites such as *Schistosoma cercariae* (Steinberg and McClenahan, 1955). By means of *in vivo* perfusion experiments using glass spheres 20 to 40 times the diameter of the lumen of capillaries, Prinzmetal, Ornitz, Simkin, and Bergman (1948) have demonstrated arteriovenous shunts in the lungs, and in most other organs, in many mammals. In most organs, therefore, there are available two normal routes for the circulation of blood—through capillaries, or through arteriovenous shunts by-passing the capillary bed. The distribution of these normal arteriovenous shunts in the human lung has been charted in fresh post-mortem specimens (Tobin and Zariquiey, 1950). These shunts are most numerous at the apices of the segmental subdivisions, in the visceral pleura, and at the level of the respiratory bronchioles.

The relationship between anatomical arteriovenous shunts and pathological arteriovenous fistulae is conjectural. The latter almost certainly develop on the basis of a generalized congenital vascular hypoplasia. Pulmonary arteriovenous fistulae have been found in the newborn, but they are usually recognized for the first time after puberty, and may have developed as a consequence of increase in pressure (Barnes, Fatti, and Pryce, 1948) such as that produced by coughing or by mitral stenosis, bursting through hypoplastic septa between artery and vein. Hypoplastic vessels forming anatomical arteriovenous shunts may distend, rupture, and coalesce to form clinically significant lesions; or the development of fistulous communication may be quite distinct from anatomical shunts. The lesions usually abut on the visceral pleura (Sloan and Cooley, 1953), where normal shunts are frequent. Pulmonary arteriovenous fistulae are not simply distended sacs fed by an end artery and drained by a vein, but are part of an intricate vascular anomaly affecting additional neighbouring vessels, and sometimes even the chest wall (Steinberg and McClenahan, 1955).

The lesion is related pathologically to haemangiomatous malformations elsewhere in the body. It is formed of two basic constituents—vascular channels lined with endothelium, and supporting connective-tissue stroma. The vascular channels range in size from structures of capillary diameter to huge saccular, multiloculated dilatations with walls of varying thickness. The amount of connective-tissue stroma varies considerably, but in clinically significant fistulae it is usually scanty. The walls of such fistulae are often so thin that, where they abut on the pleural surface of the lung, they are transparent. Small calcific plaques have been found within the fistulae (Sloan and Cooley, 1953).

The arterial supply and the venous drainage are capricious. The major arterial supply is usually from one or more branches of the pulmonary artery. Arterial blood may enter the fistula from the systemic circulation, through bronchial arteries (Baker and Trounce, 1949; Lawrence and Rumel, 1950),

directly from the aorta (Watson, 1947), or from intercostal arteries (Prutzman and Flick, 1954); or entirely unconventional vessels may contribute to the fistula (Lawrence and Rumel, 1950; Steinberg and McClenahan, 1955). The venous drainage is into the left atrium, nearly always through anatomically recognizable pulmonary veins, but aberrant venous trunks have been found (Grishman, Poppel, Simpson, and Sussman, 1949). Veins and arteries from

TABLE II

*Physical Effects of Systemic and of Pulmonary Arteriovenous Fistulae*

| | *Systemic arteriovenous fistula* | *Pulmonary arteriovenous fistula* |
|---|---|---|
| Total blood volume | Increased | Increased |
| Total plasma volume | Increased | Normal |
| Haematocrit level (%) | Normal | Increased |
| Arterial oxygen saturation | Normal | Decreased |
| Cardiac output | Increased | Usually normal |
| Cardiac enlargement | Present | Usually absent |
| Blood-pressure | High pulse pressure | Normal |
| Pulse-rate | Increased | Normal |

normal adjacent lobes may flow into the sac (Lindskog, Liebow, Kausel, and Janzen, 1950). A parallel series of direct shunts may connect artery and vein (Sloan and Cooley, 1953). The arterial supply is often reduced to the calibre of an arteriole before it enters the fistula. This is clearly shown in a low-melting alloy cast of a specimen described by Steinberg and McClenahan (1955). There is a case report of a boy of 13 years, who had arteriovenous fistulae in the middle and lower lobes, with extensive collaterals from the eighth, ninth, and 10th intercostal arteries, and collaterals extending through the diaphragm to communicate with a haemangioma of the liver (Stork, 1955). Occasionally the fistula and the adjacent lung may be found at thoracotomy to be densely adherent to the parietes by such vascular adhesions that the development of a secondary or adventitious blood-supply is suggested. The arteries and veins serving the fistula are usually considerably dilated, and this dilatation extends for a varying distance towards the heart. As in systemic congenital and traumatic arteriovenous fistulae, the vessel walls are usually very much thinner than normal.

The presence of an arteriovenous fistula within the lung does not seem to disturb the adjacent pulmonary tissue. There is no report of associated pulmonary atelectasis, infection, or bronchiectasis. In post-operative specimens the demonstration of the fistula is best achieved by an injection-corrosion technique, such as that described by McClenahan and Vogel (1952). A metal alloy of low melting point, or rubber, is used to fill the vessels, and the surrounding tissues are then digested with strong alkali.

The essential lesion in clinically significant pulmonary arteriovenous fistulae is a more or less direct communication between afferent and efferent vessels, creating a shunt which by-passes the pulmonary capillary bed, permitting the return of unoxygenated blood to the heart. The pressure in such a fistula is

usually low, but may be increased where systemic vessels contribute, possibly causing greater danger of rupture.

*Physiology*

The extent of dislocation of circulatory physiology varies in the reported cases of pulmonary arteriovenous fistulae, and depends on the size of the right-to-left shunt. The physiological effects of large pulmonary and systemic arteriovenous fistulae are contrasted in Table II (Maier, Himmelstein, Riley, and Bunim, 1948; Ronald, 1954; Weiss and Gasul, 1954). One large, several small, and many minute fistulae may produce the same physiological disturbance.

Peripheral vasodilatation may accompany an increase in total blood volume (Barnes, Fatti, and Pryce, 1948), and this may account for the normal blood-pressure in pulmonary arteriovenous fistulae. Peripheral vasodilatation and arterial oxygen unsaturation are together probably responsible for the clubbing of the fingers, which is a common clinical feature. The percentage of right ventricular output shunted through the fistula shows a wide variation in reported cases. In six cases discussed by Sloan and Cooley (1953) the shunt ranged from 18 per cent. to 89 per cent. of the right ventricular output. It is believed that in the otherwise normal subject 30 per cent. of the blood must be shunted past the pulmonary capillary bed before clinically detectable cyanosis will develop (Moyer and Ackerman, 1948; Alexander and Harrington, 1955). With a pulmonary arteriovenous fistula, breathing pure oxygen may increase the arterial oxygen saturation a little, but should not return the figure to normal (Muri, 1955). Arterial oxygen unsaturation, within certain limits of anoxia, stimulates the erythropoietic elements of the bone-marrow, producing polycythaemia (Hurtado, Merino, and Delgado, 1945). The elevation of total blood-volume is due to an increase in only red-cell volume. This response of the haematopoietic system is similar to that produced by high altitudes. The highest red-cell count recorded with a pulmonary arteriovenous fistula is 11,400,000 per cu. mm.

A pulmonary arteriovenous fistula is a right-to-left extracardiac shunt, allowing unoxygenated blood to enter the left auricle. The circulatory dynamics are therefore the same as in anomalies of venous return to the left auricle. The diagnosis can be made by cardiac catheterization. Friedlich, Bing, and Blount (1950) described the findings in four cases investigated in this way. Peripheral arterial oxygen saturation ranged in their patients from 63 per cent. to 86 per cent. The pulmonary arterial pressure and the systemic blood-flow in three of their patients were normal, and in these there was no cardiac enlargement. The fourth patient was found to have an increased cardiac output, and had moderate cardiac enlargement. In all four cases the pulmonary vascular resistance was nearly twice the normal value. The vascular resistance offered by the fistula varied. In one it was equal to that of the normal pulmonary vascular bed, in two it was nearly twice the normal, and in one it was lower than normal. It is well known that systemic arteriovenous fistulae decrease total systemic

resistance, and therefore increase the work of the heart, with increased cardiac output and size. The vascular resistance of the lungs, however, is normally so low (3 to 5 mm. Hg per litre per minute per sq. m.) that the presence of a shunt in parallel with the pulmonary resistance does not significantly reduce the overall vascular resistance of the lung, unless the vascular resistance of the shunt is unusually low. The effect of increase in the overall vascular resistance of the lungs is to increase the shunt from right to left through the fistula, to decrease the effective pulmonary blood-flow, and hence to increase the degree of systemic arterial unsaturation. A similar increase in pulmonary resistance has been described in many congenital cardiac malformations (Griswold, Bing, Handelsman, Campbell, and LeBrun, 1949). The reason for the increase in pulmonary vascular resistance exclusive of the fistula is not known. It is only where the pulmonary lesion is associated with mitral stenosis that there is reason to inculpate an increase in left atrial pressure. Allowance has been made in the calculation for elevation in resistance produced by an increase in blood viscosity due to polycythaemia. Two factors may play a role in increasing the resistance of the lungs exclusive of the fistula. Rich (1948) suggested that the increased pulmonary resistance may be due to small and multiple thrombi, such as have been described in the tetralogy of Fallot, in which there is also polycythaemia and a reduced effective pulmonary blood-flow. Motley, Cournand, Werko, Himmelstein, and Dresdale (1947) described a mechanism whereby hypoxaemia produces pulmonary arteriolar constriction. If this is the case, a vicious circle may be established: peripheral arterial oxygen unsaturation augments pulmonary arteriolar resistance, increasing blood-flow through the fistula, and so further increasing peripheral arterial oxygen unsaturation. The assessment of the circulatory dynamics in patients with pulmonary arteriovenous fistulae is described in detail by Gray, Lurie, and Whittemore (1952).

Although the heart is usually normal in patients with pulmonary arteriovenous fistulae, it is important to recognize that it may enlarge when the resistance offered to flow through the fistula is unusually low. Sloan and Cooley (1953) recorded eight cases in which the heart was enlarged, and in seven of these the electrocardiogram showed right axis deviation.

When the contribution to a pulmonary arteriovenous fistula from the systemic circulation is large in comparison with the pulmonary arterial contribution, the features of the disease attributed to anoxaemia are slight, and the danger of bleeding from the fistula is said to be greater because of the greater pressure within it (Maier, Himmelstein, Riley, and Bunim, 1948; Steinberg and McClenahan, 1955).

The experimental formation of pulmonary arteriovenous fistulae in dogs (Blalock, 1946; Takaro, Essex, and Burchell, 1951), by end-to-end anastomosis of pulmonary artery and vein after lobectomy, produces in survival studies a clinical state of polycythaemia, dyspnoea on exertion, cyanosis, and arterial oxygen unsaturation varying from 60 to 90 per cent. Takaro, Essex, and Burchell (1951) were unable to establish any relationship between arterial oxygen unsaturation and cardiac output in the hypoxaemic dogs.

### *Clinical Picture*

*Number of cases.* The three largest series reported are those of Sloan and Cooley (1953), Weiss and Gasul (1954), and Steinberg and McClenahan (1955); each of these groups presented a small personal series, and together they collected about 350 recorded cases. Altogether more than 400 cases have now been recorded. The lesion remains relatively uncommon. In 2,000 consecutive angiograms Steinberg and McClenahan (1955) found only nine pulmonary arteriovenous fistulae.

*Presentation.* Most patients come under observation because of some or all of the classical clinical features. Some are found to have isolated pulmonary opacities during mass radiographic surveys or other routine radiography. In many cases detected in this way the clinical features have previously escaped observation. A few patients are first seen with one of the complications. The lesion is most commonly confused with cyanotic heart disease, or with polycythaemia vera (Muri, 1955).

*Clinical features.* The classical features are cyanosis, clubbing of the fingers, polycythaemia, dyspnoea, and an extracardiac murmur. In addition, the heart is usually normal, and cutaneous and mucosal haemangiomata are frequent. Bleeding from the respiratory tract—usually as epistaxis from nasal mucosal telangiectases, less often as haemoptysis—is not uncommon. A variety of central nervous symptoms has been described, and the frequency with which these symptoms are encountered varies from one series to another. Osteoarthropathy, a history of squatting (Lindskog, Liebow, Kausel, and Janzen, 1950; Tobin and Zariquiey, 1950), and pain in the chest, have all been recorded, but are rare. Some of the lesions are asymptomatic. The number of male patients recorded is slightly higher than the number of female patients. No special racial incidence is known. There is a family history of pulmonary arteriovenous fistula in a small percentage of cases, and a family history of hereditary haemorrhagic telangiectasis in about 15 per cent. The diagnosis is usually made in the third to the fifth decade, but the lesion has been found in the newborn (Bowers, 1936), and in the very old. Many patients have had symptoms for many years without being seriously disabled, and the symptoms are often not progressive, suggesting that the natural history of the lesion is prolonged and relatively benign (Sloan and Cooley, 1953).

Any part of the lung may be the site of a fistula. More have been found in the right lower lobe than elsewhere, and the lower lobes together are affected more frequently than the rest of the lung. The lesions are commonly multiple, and commonly bilateral. All five lobes may be affected (Adams, Thornton, and Eichelberger, 1944). It is of great importance therapeutically to recognize that multiple lesions are common, and that not all the fistulae may be clearly seen on ordinary radiographs.

Cyanosis is a consequence of the shunting of unoxygenated blood past the pulmonary capillary bed. Polycythaemia results from the stimulation of erythropoiesis by anoxia. Clubbing of the fingers and toes is probably related

to cyanosis and peripheral vasodilatation. Cyanosis and plethora are usually out of proportion to the dyspnoea, which is often mild. Patients who have bled from pulmonary or other haemangiomatous lesions may be anaemic rather than plethoric when first seen.

The murmur is either continuous with systolic accentuation, or only systolic. It may be heard only at the end of deep inspiration, and is commonly augmented by deep inspiration. A thrill is rare. Expiration against a closed glottis after full inspiration (the Valsalva manœuvre) increases intrathoracic pressure and diminishes flow through the lungs, including the fistula, and the murmur may disappear. Deep inspiration against a closed glottis after full expiration (the Müller manœuvre) decreases intrathoracic pressure; more blood flows through the fistula, and the murmur may be increased.

Protean manifestations of central nervous disorder have occurred: headache, vertigo, weakness, faintness, dizziness, diplopia, epilepsy, convulsions, visual and auditory disturbances, numbness, speech defects, transient paresis, paraesthesia, and even hemiplegia. They are attributed to cerebral anoxia, an expression of arterial oxygen unsaturation; to polycythaemia, with its tendency to thrombus formation; to air embolism, the air gaining access to the circulation through defects in the wall of the fistula; to cerebral angiomatous malformations; and to cerebral abscess. The association between pulmonary arteriovenous fistula and cerebral lesions, especially cerebral abscess, is discussed later, with the complications.

A heart of normal size, with a normal electrocardiogram, is usual with pulmonary arteriovenous fistula, but cardiac enlargement without detectable intracardiac abnormality has been reported (Sisson, Murphy, and Newman, 1945; Boerema and Brilman, 1948; Wodehouse, 1948; Baker and Trounce, 1949; Friedlich, Bing, and Blount, 1950; Lawrence and Rumel, 1950). In those patients with cardiac enlargement in whom catheter studies have been made, an increase in cardiac output has been demonstrated, and the resistance offered to the flow of blood through the fistula has been sufficiently low to reduce considerably the total pulmonary vascular resistance.

Of the patients reported in the literature, approximately 75 per cent. have had clubbed fingers and cyanosis; approximately 50 per cent. have had dyspnoea, and were found to be polycythaemic and to have a murmur; approximately 25 per cent. have had a history of bleeding (usually epistaxis); and a similar percentage have been found to have central nervous disorders. In about 30 per cent. of the cases reported there is no mention of one or more of these cardinal features.

*Radiographic features.* A pulmonary opacity is the most constant of the abnormal findings. Rarely patients have been reported (Brink, 1950; Cooley and McNamara, 1954) with normal chest radiographs and unequivocal evidence of a large right-to-left shunt, with a normal heart, no murmur, and equivocal angiograms. These patients (one of them at thoracotomy) have been found to have numerous very small pulmonary arteriovenous fistulae. They have shown, in addition, all the evidence of multiple familial haemorrhagic telangiec-

tasis. The typical radiographic opacity is a rounded or lobulated homogeneous opacity within the lung parenchyma, with fairly well defined margins, and bound to the pulmonary hilum by cord-like extensions which are the shadows of dilated subserving vessels. Calcification within the opacity is uncommon, but has been reported (Jones and Thompson, 1944; Sloan and Cooley, 1953). Behind the X-ray screen the opacity may be seen to pulsate, as may the vascular extensions. It may alter in size with the Valsalva and Müller manœuvres, diminishing with the former and increasing with the latter. Impressive pulsation of the opacity on screening has been seen in about half of the cases reported (Lindskog, Liebow, Kausel, and Janzen, 1950; Sloan and Cooley, 1953). Pulsation may be absent because of clot within the fistula (Stork, 1955). Rib notching, suggestive of a large contribution to the fistula from dilated intercostal vessels, has been observed. Stork (1955) reported three such cases. Makler and Zion (1946) have observed increase in the size and number of radiographic opacities in a patient with all the supporting evidence of pulmonary arteriovenous fistulae.

*Angiocardiography.* It is an essential preliminary to surgical treatment to outline all the fistulae with opaque medium, so that fistulae are not left behind at operation. A radiographic opacity which is not convincingly filled with dye may yet be a fistula, since the blood within the fistula may have clotted. Small fistulae, unsuspected on plain films, and even imperfectly demonstrated on angiograms, have been known to grow and reproduce the clinical syndrome after excision of large fistulae has relieved the symptoms (Adams, Thornton, and Eichelberger, 1944; Charbon, Adams, and Carlson, 1952). Large films must be made, to include the whole lung field, in order to avoid missing multiple and bilateral fistulae. Minute fistulae may not be satisfactorily demonstrated with good angiograms (Cooley and McNamara, 1954). The opaque medium often persists within the fistula and its vascular connexions long after it has cleared from the rest of the lung (Lindskog, Liebow, Kausel, and Janzen, 1950). Angiocardiography carries with it a certain risk. There are two reports (Runström and Sigroth, 1950; Sloan and Cooley, 1953) of brisk haemoptysis following injection of the dye. Rupture of the heart has occurred (Starkey and Milstein, 1953), and death from pulmonary oedema within 25 minutes of dye injection (Sisson, Murphy, and Newman, 1945). Better pictures are usually obtained by selective injection into first one and then the other pulmonary artery, and four injections, one for each lung, in the lateral and anteroposterior positions, give the most satisfactory results. The limit of safe exposure to X-rays may be very closely approached in these patients, who have usually had many radiographs.

*Familial incidence.* There are numerous reports of pulmonary arteriovenous fistulae in more than one member of the same family: in sisters (Glenn, Harrison, and Steinberg, 1953; Steinberg and McClenahan, 1955; O'Neill, Fisher, McDowell, and Lauby, 1956); in brothers (Goldman, 1948; Moyer and Ackerman, 1948); in father and son (Tobin and Wilder, 1953); in father and daughter (Sloan and Cooley, 1953); in mother and son (Heyde, 1954). Stringer, Stanley,

Bates, and Summers (1955) had knowledge of five examples of fistulae in one family.

*Association with hereditary haemorrhagic telangiectasis* (*Rendu–Osler–Weber disease*). Hereditary haemorrhagic telangiectasis is a congenital vascular abnormality, transmitted as a simple Mendelian dominant, not sex-linked, but slightly commoner in women. The lesions are commonest on the skin of the face and neck, and on the buccal and nasopharyngeal mucous membranes. Epistaxis is the commonest symptom, and usually appears after puberty. The lesion is fundamentally a defect of development of the terminal loops of capillaries, and haemorrhage is a consequence of abnormal fragility of these defective vessels (O'Neill, Fisher, McDowell, and Lauby, 1956). Coagulation time, bleeding time, platelet count, and fragility tests are normal. There may be telangiectases in any of the abdominal viscera, in the mucosa of the alimentary tract, in the lungs, in the mucosa of the respiratory and genito-urinary tract, and in the brain and spinal cord. Any of these lesions may bleed. There is some overlap between the syndromes of haemorrhagic telangiectasis, hereditary familial vascular purpura, and pseudo-haemophilia (Wells, 1946). A family history of hereditary haemorrhagic telangiectasis is found in about 15 per cent. of patients with pulmonary arteriovenous fistulae. About 40 per cent. of patients with pulmonary arteriovenous fistulae have in addition mucosal or cutaneous telangiectasis. It is likely that pulmonary arteriovenous fistulae are manifestations of a generalized vascular dysplasia closely related to, or part of, the disease of hereditary haemorrhagic telangiectasis (Freedman, Hensler, and Pollock, 1952; Israel and Gosfeld, 1953; Sloan and Cooley, 1953; Weiss and Gasul, 1954; Steinberg and McClenahan, 1955). It is therefore important to obtain chest radiographs in all patients exhibiting evidence of this angiodysplastic disorder.

*Association with mitral stenosis.* Steinberg and McClenahan (1955) and Lindgren (1946) quoted examples of pulmonary arteriovenous fistulae in patients with mitral stenosis. Three of the six patients reported in the present paper had mitral stenosis. In two of these patients the mitral stenosis was diagnosed clinically and demonstrated surgically to be severe; in the third it was estimated clinically to be mild. The relationship between mitral stenosis and the development or enlargement of pulmonary arteriovenous fistulae is not known. Pulmonary hypertension, a consequence of mitral stenosis, may result in the rupture of hypoplastic vascular septa in a patient with a generalized vascular dysplasia, or may increase the size of the shunt through an already established pulmonary arteriovenous fistula.

### *Diagnosis*

Diagnosis in the first instance depends on bearing in mind the possibility of pulmonary arteriovenous fistula being the cause of any one of the typical or less usual clinical features, many of which are common to a variety of diseases. Once suspected, the diagnosis can nearly always be established by screening,

tomography, and angiography. Differentiation from cyanotic heart disease is made by accurate interpretation of clinical findings and special investigations, especially cardiac catheterization. Differentiation from polycythaemia vera is usually not difficult. The white-cell count and the spleen are normal in cases of pulmonary arteriovenous fistulae, and although pulmonary opacities are occasionally found in polycythaemia vera—caused, it is believed, by intravascular clotting—these opacities change their character and tend to clear (Hirsch, 1936; Weiss and Gasul, 1954). Patients with opacities detected by mass radiographic surveys tend to accumulate in sanatoria, and awareness of the occurrence of pulmonary arteriovenous fistulae is of special importance for those interpreting mass X-rays, and for those who deal with the patients found to have abnormal X-rays during mass surveys.

### *Complications*

Haemorrhage, infection, and cerebral lesions may complicate pulmonary arteriovenous fistulae. Bleeding is a common symptom, but is usually from telangiectases in the nose. Haemoptysis is considerably less common, but may be the presenting symptom (Janes, 1944) and may be the cause of death (Israel and Gosfeld, 1953; Heyde, 1954). Massive pleural haemorrhage is still less common. Bowers (1936) reported a case of fatal pleural haemorrhage from a pulmonary arteriovenous fistula in a baby of two days. Boerema and Brilman (1948) described the case of a boy, cyanotic from birth, who had frequent convulsive seizures. Haemoptysis was a frequent occurrence, and on one occasion haemoptysis and convulsions occurred simultaneously, suggesting the possibility of air embolism following upon rupture of the pulmonary vessel. Bacterial endarteritis and septicaemia have been reported (Maier, Himmelstein, Riley, and Bunim, 1948; Stevenson, 1953). There may be some relationship between infection in the fistula and cerebral abscess. Chemotherapy has controlled two reported cases of bacterial endarteritis. A patient reported by Ronald (1954) died during a Stokes–Adams attack.

The cerebral symptoms previously enumerated are reported by some observers to be frequent. Alexander and Harrington (1955) claimed that 30 per cent. of patients have cerebral symptoms at some time, and Yater, Finnegan, and Giffin (1949) reported 45 cases with cerebral symptoms. In some large series cerebral symptoms have been much less common. Ten published examples of pulmonary arteriovenous fistula complicated by cerebral abscess have been found (Wodehouse, 1948; Muri, 1953; Stern and Naffziger, 1953; Chambers, 1955; Steinberg and McClenahan, 1955). Cerebral abscess in cyanotic heart disease is not uncommon, and it is likely that the mechanism for the production of cerebral symptoms and cerebral abscess in the two diseases is the same. A variety of mechanisms has been suggested:

1. Polycythaemia may cause the precipitation of thrombi *in situ* (in the brain),

or of thrombi elsewhere, with subsequent cerebral embolism. Cerebral symptoms and signs occur in polycythaemia vera with or without manifest cerebral thrombosis of large size.

2. Cerebral angiomatous malformations may occur as a part of the syndrome of hereditary haemorrhagic telangiectasis. They may produce symptoms by pressure or by rupture. No published report has been found of pulmonary and cerebral arteriovenous fistulae occurring in the same patient.

3. The pulmonary lesion may impair the filtering effect of the lungs, allowing sterile or septic emboli arising in the periphery to reach the brain. The filtering effect of the lungs in normal circumstances is probably not entirely adequate. The normal anatomical arteriovenous shunts in the lungs probably allow the passage of large particles such as tumour cells, parasites, or fat emboli after fractures.

4. Cerebral anoxia, the result of arterial oxygen unsaturation, may produce impairment of cerebral cell function without histologically detectable cellular abnormality. Focal necrosis of cerebral tissue may also result from anoxia in the absence of vascular occlusion (Berthrong and Sabiston, 1951).

5. Cerebral abscess may result from septic emboli lodging in the brain, or from secondary infection in areas of brain damaged by anoxia or vascular occlusion. The infecting organism has sometimes been *H. influenzae*—an obligatory anaerobe growing best in 10 per cent. of $CO_2$, and needing haemoglobin in the culture medium. Small areas of brain damaged by anoxia, or by thrombosis due to polycythaemia, in a cyanotic patient, would be an ideal culture medium (Wodehouse, 1948). *H. influenzae* is a common commensal organism in the upper respiratory tract. Brain abscess in Fallot's tetralogy has been reported after tonsillectomy or tooth extraction.

6. Air embolism may occasionally be the cause of cerebral symptoms.

### *Treatment*

The only treatment available is surgical, and the operation of choice is the most limited resection compatible with complete removal of the fistula. Even when only one fistula has been demonstrated by detailed investigation, including angiocardiography, a lobe should not be sacrificed when segmental resection might suffice, and a segment should not be removed when excision of the fistula alone is possible, because of the danger of small and previously unsuspected fistulae becoming clinically important in later years (Weiss and Gasul, 1954). The induction of a pneumothorax used to be a method of treatment. The size of fistulae and the course of the disease were in no way influenced (Hepburn and Dauphinee, 1942). Radiotherapy has been used, sometimes because the pulmonary opacity has been misdiagnosed as a pulmonary tumour (Jones and Thompson, 1944), also without any effect on the fistula. There is no problem regarding the advice to give a patient with one fistula or few fistulae producing symptoms, provided the surgical risk is a reasonable one. The fistulae should be excised. The decision as to treatment is more difficult where fistulae are

small and asymptomatic, with a small shunt and normal arterial oxygen saturation, or where there are extensive and multiple fistulae, the complete excision of which is likely to deprive the patient of large volumes of lung.

In the case of small asymptomatic fistulae it is probably safe merely to keep the patient under observation. This view was not supported by Steinberg and McClenahan (1955), who believed that even the asymptomatic fistulae should be removed because of the danger of complications, nor by Muri (1955), who stressed the fact that the course of the disease is one of enlargement of the fistula. There is admittedly always the danger of a single catastrophic haemorrhage, or of infection, but with small fistulae the likelihood of either is remote. Cerebral complications are also not a feature of small asymptomatic fistulae. The age of the patient is probably the factor most likely to influence the decision whether or not to excise a small asymptomatic fistula: in the young it is usually decided to remove the fistula, and in the old it is likely to be left alone. The published reports of series observed without operation (Sloan and Cooley, 1953; Muri, 1955) do not make it clear how many of the patients observed were asymptomatic, and for how long they were observed. But of 90 patients not submitted to operation, 50 remained well, 20 died from unrelated causes, or from some investigatory procedure, 12 died from rupture into a bronchus or into the pleural space, and eight died from brain abscess. The mortality from operation in a number of series averages about 8 per cent.

Where fistulae are bilateral, removal of the lesions from one lung is usually followed by clinical improvement for only a short time, after which the residual fistulae increase in size, with reversion to the pre-operative state (Baer, Behrend, and Goldburgh, 1950; Charbon, Adams, and Carlson, 1952). In individual patients with bilateral lesions, bilateral sternal-splitting thoracotomy may be worth considering. This technique is successfully used in some centres for the excision of bilateral tuberculous lesions of the lungs (Lewis, Shumway, Taufic, Zimmerman, Perry, Cohen, and Ring, 1956).

The early patients reported (Hepburn and Dauphinee, 1942; Adams, Thornton, and Eichelberger, 1944) were all submitted to pneumonectomy. At least one of these patients developed contralateral fistulae at a later date. Charbon, Adams, and Carlson (1952) described the excision of fistulae from the remaining lung of such a patient seven years after pneumonectomy for arteriovenous fistula. Lobectomy and segmental resection are frequently undertaken. Wedge resection of the fistula has been the technique employed in some cases. Ligation of vessels supplying and draining the fistula has also been undertaken (Packard and Waring, 1948; Muri, 1955), but fistulae treated in this way have been reported to recur, and later to require segmental resection (O'Neill, Fisher, McDowell, and Lauby, 1956). The fistula becomes flaccid and empty, and ceases to pulsate, when all the afferent and efferent vessels have been controlled. The bulging, pulsating vascular sac, with blood swirling, streaming, and eddying within it, clearly visible through the thin sac wall, is an impressive sight at operation, commented on by many observers (for example, Carswell, 1950). Systemic vessels contributing to the fistula have been ligated together

with pulmonary vessels, without recurrence of the fistula. Stripping out the fistula, after ligation of all its vessels, without the sacrifice of any lung tissue, has been undertaken, and must be the method of choice where it is possible.

In the early post-operative period deep vein thrombosis is said to be common in patients with polycythaemia (Maier, Himmelstein, Riley, and Bunim, 1948). Assiduous long-term observation of patients submitted to resection of fistulae is essential if the development of further fistulae is to be recognized and treated.

*Summary*

Six cases of pulmonary arteriovenous fistula are reported. The morbid anatomy and physiology of the disease are discussed, the clinical and radiographic features described, and the complications enumerated. Limited surgical resection is advocated in patients with symptoms.

*Addendum* (*Case 3*). The patient returned recently with increasing haemoptysis; mitral valvulotomy and resection of her fistulae were undertaken at one operation through a trans-sternal approach, and she is now entirely well (July 1958).

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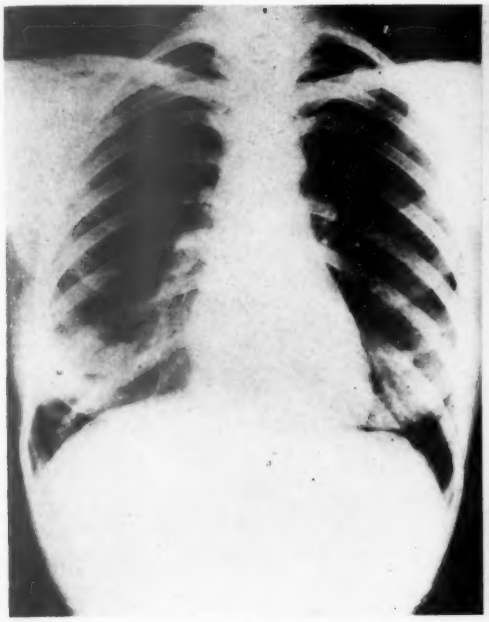

FIG. 1.

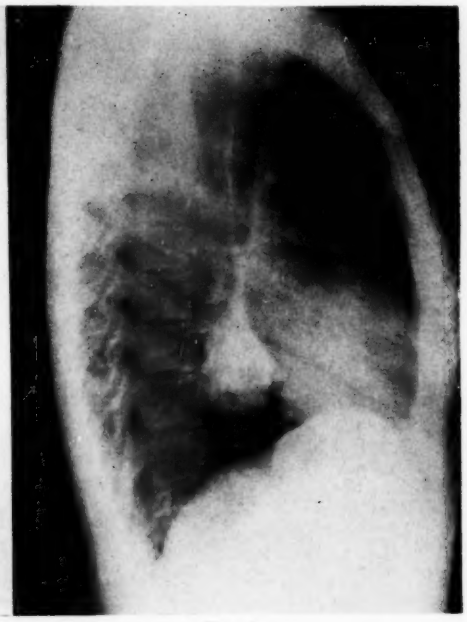

FIG. 2.

FIGS. 1 and 2. Case 1. Postero-anterior and lateral views of the chest, showing the lobulated opacity below the pulmonary hilum and connected to the hilum by large vascular shadows

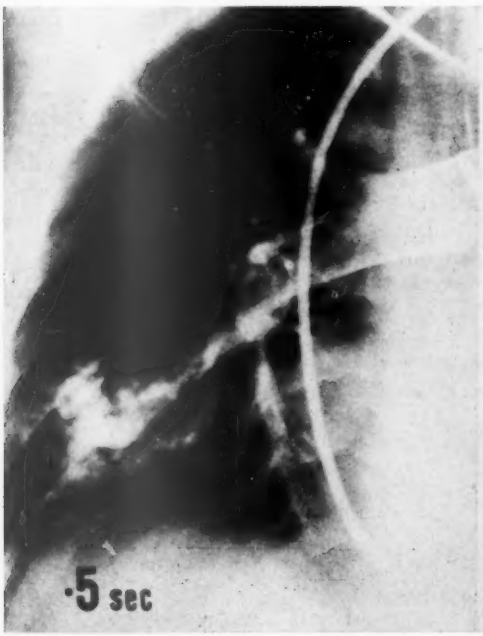


FIG. 3. Case 1. Angiogram showing the arteriovenous fistula in the right lower lobe outlined at 0·5 second


FIG. 4. Case 1. The venous drainage of the fistula best outlined at 1·5 second


FIG. 5. Case 1. A rubber cast of the excised fistula


FIG. 6. Case 2. An angiogram showing the fistula outlined at 2 seconds

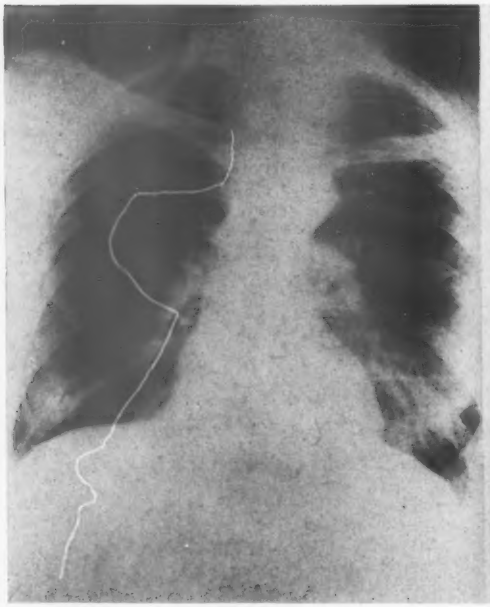

FIG. 7.

FIG. 8.

FIGS. 7 and 8. Case 2. Postero-anterior view of the chest and tomogram, showing the fistula and its vascular extension towards the pulmonary hilum

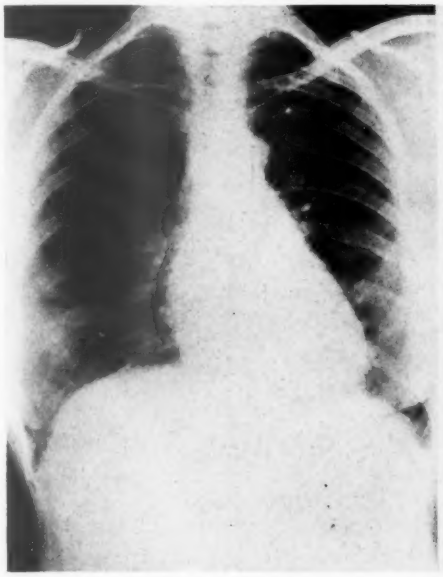

FIG. 9.

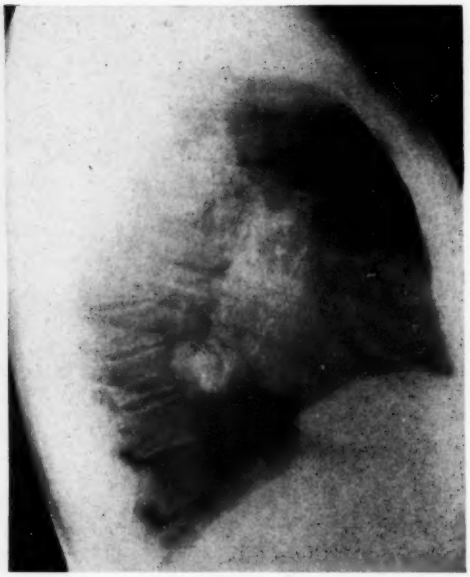

FIG. 10.

FIGS. 9 and 10. Case 3. Postero-anterior and lateral views of the chest, showing the largest fistula

FIG. 11. Case 3. Tomogram demonstrating the lobulation and hilar connexion of the fistula

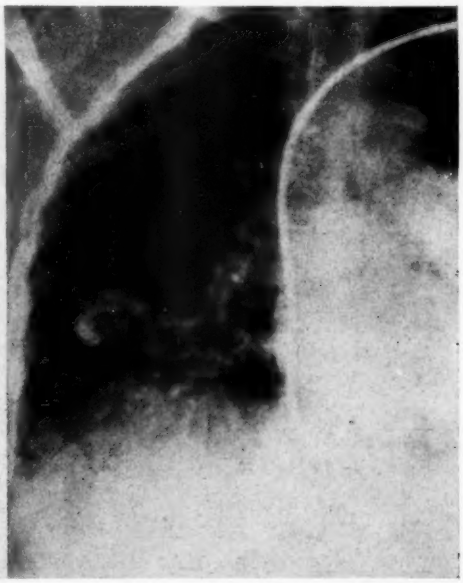

FIG. 12. Case 3. An angiogram showing the largest fistula. The two smaller ones are not seen in this view

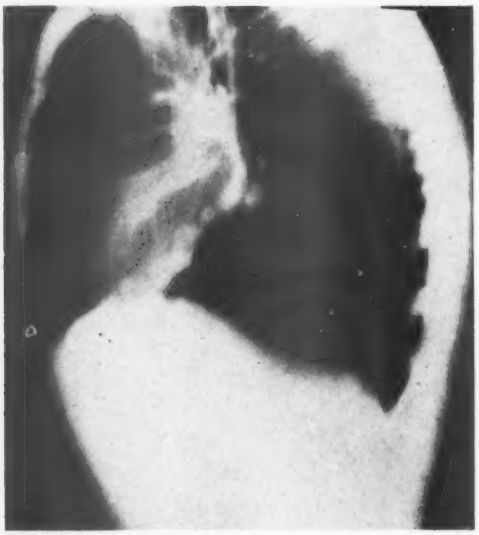

FIG. 13. Tomograms made of the left fistula in Case 4 before mitral valvulotomy and excision of the fistula

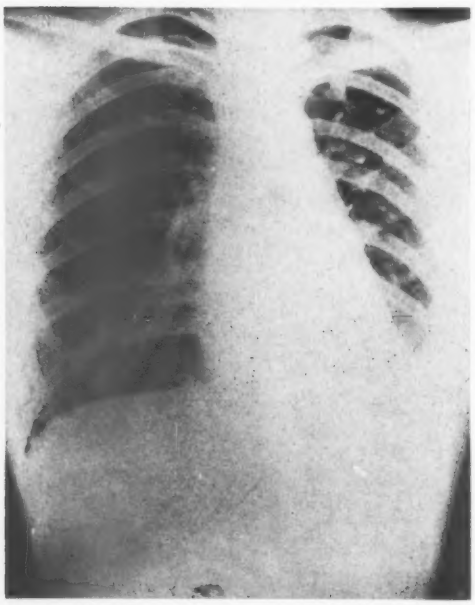

FIG. 14. Postero-anterior view of the chest made before excision of the right fistula in Case 4

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# THE PATHOGENESIS OF ANAEMIA AFTER PARTIAL GASTRECTOMY

## I. DEVELOPMENT OF ANAEMIA IN RELATION TO TIME AFTER OPERATION, BLOOD LOSS, AND DIET[1]

By I. McLEAN BAIRD, E. K. BLACKBURN, and G. M. WILSON

(From the Department of Pharmacology and Therapeutics, University of Sheffield, and the Department of Haematology, United Sheffield Hospitals)

Deganello (1900) described a patient with *cancer diffus* of the stomach who developed iron-deficiency anaemia after total gastrectomy. Subsequently systematic studies of anaemia after partial gastrectomy were made by Morley (1928) and Gordon-Taylor, Hudson, Dodds, Warner, and Whitby (1929). Morley observed that 12 out of 21 patients became anaemic after the Polya operation, and only four out of 21 patients were anaemic after the Schoemaker operation. In the Polya gastrectomy anastomosis is made between the gastric remnant and the jejunum, whereas in the Schoemaker or Billroth I gastrectomy gastroduodenal continuity is maintained by anastomosis of the gastric remnant to the duodenum. Hartfall (1934) reported anaemia in 50 per cent. of women and 16 per cent. of men in a group of 91 patients who had had a Polya gastrectomy. He noted a high incidence of vomiting and diarrhoea in the anaemic patients, and observed 'one could hardly fail to be impressed by the fact that these anaemic individuals were very frequently eating an abnormal diet, and red meat and vegetables were never taken'. The frequency of anaemia after partial gastrectomy has varied widely in reported series, depending on the haematological techniques and the definition of anaemia. Semb (1937) found that 25 per cent. of male patients and 70 per cent. of female patients became anaemic. Watson (1947) reported an incidence of 14 out of 127 (11 per cent.), and Muir (1949) showed that 9·3 per cent. of male and 20 per cent. of female patients were anaemic. Wells and Welbourn (1951) took an arbitrary haemoglobin level of 14 g. per 100 ml. as the lower limit of normal for men, and 12 g. per 100 ml. for women. With these criteria anaemia was present in 15 per cent. of men and 30 per cent. of women at periods of one to 10 years after the gastrectomy. Anderson, Gunn, and Watt (1955) found that the haemoglobin levels were subnormal in the majority of patients after partial gastrectomy, especially in women. Blake and Rechnitzer (1953) also observed that the highest incidence of anaemia after partial gastrectomy occurred in women under 50 years of age. Older women and men of all ages developed iron deficiency to a less extent.

In spite of the numerous clinical reports describing the occurrence of anaemia

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after partial gastrectomy, the mechanism of its development remains obscure. Inadequate nutrition (Hartfall, 1934), absence of gastric acidity (Capper, 1952), intestinal hurry (Wells and Welbourn, 1951), malabsorption of iron (Anderson, Gunn, and Watt, 1955), and blood loss (Witts, 1956) have all been suggested as factors in the pathogenesis of the anaemia. There is little evidence, however, to confirm these possibilities. The purpose of the present study is to examine the natural history of the anaemia and its relation to time after operation, diet, and blood loss.

Iron-deficiency anaemia is common and pernicious anaemia rare after partial gastrectomy (Gordon-Taylor, Hudson, Dodds, Warner, and Whitby, 1929). Total gastrectomy is commonly followed by macrocytic changes (Hartman, 1921; Ellis, 1925; Breitenbach, 1929; Dennig, 1929; Hochrein, 1929; Hurst, 1932; Brain and Stammers, 1951; Tomoda, 1954; Welbourn, Nelson, and Zacharias, 1956). There is still a source of intrinsic factor remaining after partial gastrectomy, and this fact may explain the rarity of pernicious anaemia in large series reported by Wells and MacPhee (1954) and Anderson, Gunn, and Watt (1955). Welbourn, Nelson, and Zacharias (1956) have suggested that pernicious anaemia is no commoner after this operation than in the general population. Girdwood (1956) reported a progressive fall in serum vitamin-$B_{12}$ levels after total gastrectomy, and this change preceded the development of megaloblastic changes in the marrow. After partial gastrectomy Lyngar (1950) found evidence of normoblastic and macronormoblastic maturation arrest in the bone-marrow. This aspect of the problem has been studied further, and the bone-marrow changes associated with the anaemia developing after partial gastrectomy have been included in the present investigation.

## *Methods*

Names of patients on whom the operation of partial gastrectomy for peptic ulcer had been performed during the years 1940 to 1955 were obtained from the operation registers of two hospitals. Patients suffering from gastric neoplasm, and those who had undergone a total gastrectomy, were excluded. All available surviving patients were requested to attend for clinical and haematological examinations. In addition, haematological investigations were carried out in two other groups. One hundred patients admitted for a previously planned partial gastrectomy were investigated immediately prior to operation; the results of the haematological investigations were compared with those found at varying intervals after partial gastrectomy. Patients admitted on account of a recent blood loss, and emergency cases, were excluded. A further 127 patients who had chronic peptic ulceration demonstrated radiologically were chosen from the records of the X-ray department. All patients referred for X-ray investigation primarily on account of a recent gastrointestinal haemorrhage were excluded, as also were any who had received an operation on the alimentary tract. The duration of symptoms of peptic ulceration was ascertained in these patients, and a full blood examination was carried out. The results of the

haematological investigations were principally used for regression analyses to correlate haemoglobin levels with time after operation or duration of ulcer symptoms.

TABLE I

| | | |
|---|---|---|
| Total patients having partial gastrectomy in years 1940–55 | | 520 |
| Failed to attend for examination | | 119 |
| Patients examined | | 401 |
| Patients excluded from statistical analysis | | 60 |
| (*a*) Haematinic therapy or recent haemorrhage | 32 | |
| (*b*) More than 10 years after operation | 8 | |
| (*c*) Unrelated illness | 18 | |
| (*d*) Pulmonary tuberculosis | 2 | |
| Patients included in statistical analysis | | 341 |

The haemoglobin estimations were made in duplicate as oxyhaemoglobin in a grey-wedge photometer (King, Wootton, Donaldson, Sisson, and Macfarlane, 1948). Red cells, leucocytes, mean corpuscular haemoglobin concentration, mean corpuscular volume, and blood smears, were studied by standard methods (Whitby and Britton, 1953). Aspiration marrow biopsy was made from the iliac crest in selected cases. The average daily intake of iron, protein, and

TABLE II

*Mean Haematological Results in 441 Ulcer Patients, 100 Before Gastrectomy and 341 After Polya and Billroth Gastrectomies*

| | *Men* | | | | | *Women* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Number of cases* | *Haemoglobin (G./100 ml.)* | *Red cells (millions/cu. mm.)* | *Mean corpuscular haemoglobin concentration (per cent.)* | *Mean corpuscular volume (cu. μ)* | *Number of cases* | *Haemoglobin (G./100 ml.)* | *Red cells (millions/cu. mm.)* | *Mean corpuscular haemoglobin concentration (per cent.)* | *Mean corpuscular volume (cu. μ)* |
| Before gastrectomy | 50 | 15·4 | 5·2 | 31·1 | 96·2 | 50 | 12·9 | 4·2 | 32·7 | 95·4 |
| After Polya gastrectomy | | | | | | | | | | |
| 0–2 yrs. | 63 | 13·9 | 4·3 | 30·8 | 95·8 | 14 | 13·8 | 4·3 | 33·3 | 94·0 |
| 2–4 yrs. | 110 | 13·5 | 4·7 | 31·7 | 94·8 | 10 | 12·4 | 4·7 | 29·2 | 95·9 |
| 4–6 yrs. | 30 | 13·3 | 4·5 | 30·1 | 97·0 | 17 | 10·4 | 3·8 | 27·6 | 92·9 |
| 6–10 yrs. | 30 | 12·1 | 4·5 | 28·3 | 93·0 | 15 | 10·0 | 3·6 | 27·6 | 94·2 |
| After Billroth gastrectomy | | | | | | | | | | |
| 0–2 yrs. | 26 | 14·8 | 4·7 | 33·4 | 94·8 | 6 | 13·0 | 4·0 | 32·0 | .. |
| 2–4 yrs. | 5 | 14·9 | 4·9 | 31·6 | 96·8 | 5 | 12·3 | 4·0 | 31·0 | .. |
| 4–6 yrs. | 0 | .. | .. | .. | .. | 0 | .. | .. | .. | .. |
| 6–10 yrs. | 10 | 12·9 | 4·5 | 31·0 | 90·2 | 0 | .. | .. | .. | .. |

calories in the diet after partial gastrectomy was estimated by taking a detailed history and consulting dietary tables (McCance and Widdowson, 1946). Eighty patients were investigated in this way, and the diets of anaemic and non-anaemic groups were compared. Estimates of this type can at best represent only a rough approximation, but an attempt to determine their reproducibility was made in 12 patients, who, after an interval of two or three weeks, were again questioned about their diet. On the first occasion the main daily intake of iron was estimated as 12·8 mg. and on the second occasion 11·8 mg. There was no significant difference ($P > 0·7$). The presence of occult blood in the faeces was detected by Needham and Simpson's (1952) modification of the Gregerson test, using 0·5 per cent. benzidine hydrochloride.

*Results*

The attendance and selection of patients who had had a partial gastrectomy in the years 1940 to 1955 are shown in Table I. Patients who had received treatment for anaemia within the previous three months were excluded from the survey. Those with other diseases which might affect the haematological findings were also excluded. Only eight patients who had had operations more than 10 years ago, during the war years, attended for examination; as this group could not readily be increased in size it was excluded from the statistical analysis. The remaining 341 patients were studied in detail.

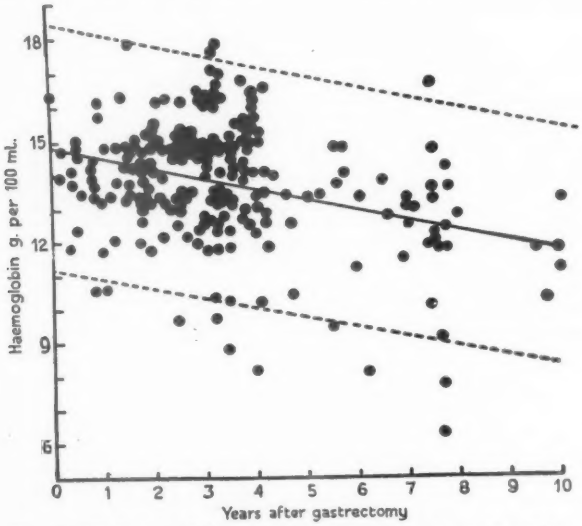


FIG. 1. The haemoglobin levels of 233 male patients after Polya partial gastrectomy, correlated with the duration of time in years after the operation. The dotted lines represent the 95 per cent. confidence limits.

*The development of anaemia after partial gastrectomy.* The mean haematological results, in patients grouped at intervals after operation, are compared with those obtained in the 100 patients with peptic ulcer examined immediately before operation (Table II). Decreases in haemoglobin, red-cell count, and mean corpuscular haemoglobin concentration are seen after operation in many of the groups. The decline in haemoglobin is apparently associated with the passage of time after partial gastrectomy, and this decline has accordingly been analysed in greater detail in relation to sex and type of operation. The haemoglobin values in 233 male patients after Polya gastrectomy are shown in Fig. 1. A regression analysis yields a highly significant correlation ($P < 0{\cdot}001$) between the fall in haemoglobin levels and the time after operation. A significant decrease was also found in the smaller group of 41 male patients after Billroth I partial gastrectomy (Fig. 2). This group, however, is small and unevenly scattered,

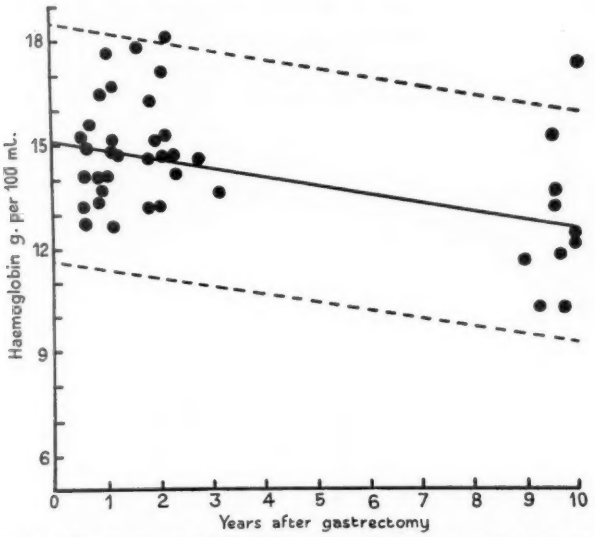


FIG. 2. The haemoglobin levels of 41 male patients after Billroth I partial gastrectomy.

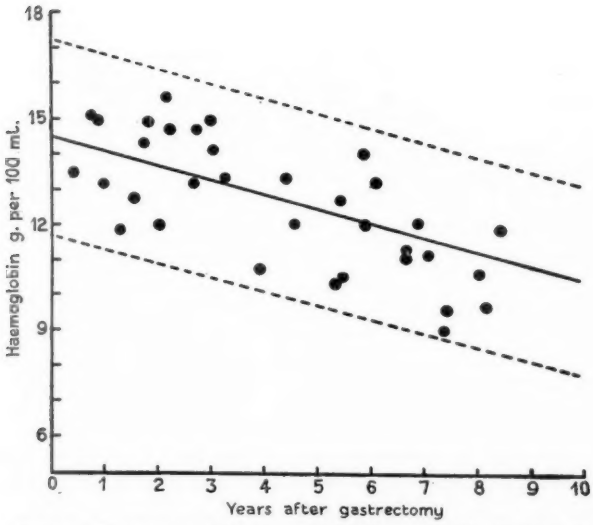


FIG. 3. The haemoglobin levels of 34 female patients over 50 years of age after either Polya or Billroth I partial gastrectomy.

owing to fluctuations in surgical opinion regarding the desirability of this operation, and, though the decline in haemoglobin is slightly less steep after the Billroth than after the Polya operation, this difference does not attain statistical significance ($P > 0{\cdot}05$). Only 11 of the 67 female patients had a Billroth I

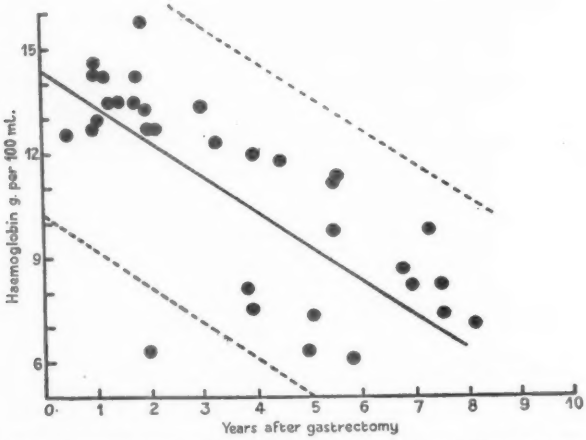


FIG. 4. The haemoglobin levels of 33 female patients under 50 years of age after either Polya or Billroth I partial gastrectomy.

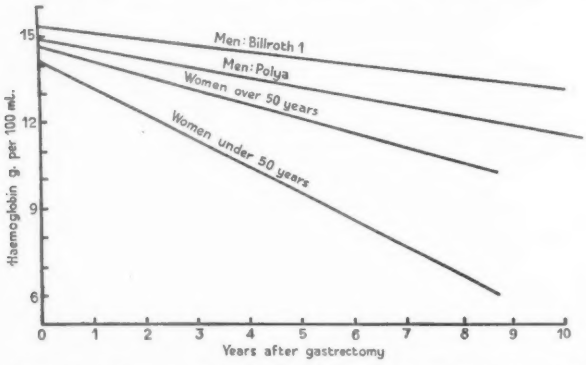


FIG. 5. The regression lines of all haemoglobin values estimated after partial gastrectomy, to show the rate of fall in the four groups.

operation, and in view of this small number both types of partial gastrectomy are considered together. As, however, menstruation is an important factor in the development of anaemia, the women have been separated on an age basis, with 50 years as the dividing point. Both groups again show a decline in haemoglobin with the lapse of time after operation, and this is particularly conspicuous in the women under 50 years of age (Figs. 3 and 4). The slope of the regression line in this latter group is significantly different from that seen in the older women ($P < 0{\cdot}001$). The slopes of all these lines are shown together in Fig. 5,

and the liability of the younger women to develop rapidly a severe anaemia after partial gastrectomy is immediately apparent.

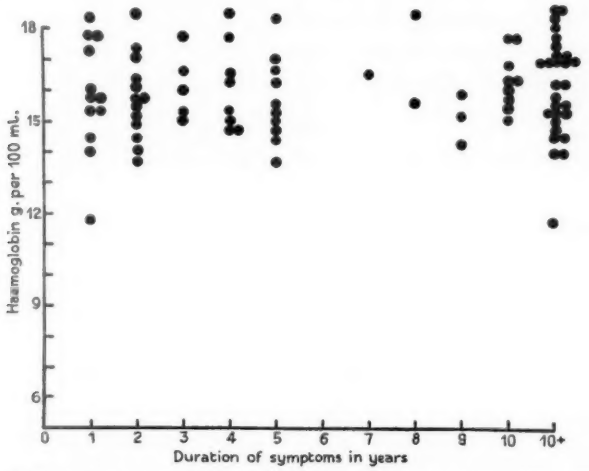


FIG. 6. The haemoglobin levels in 91 male peptic ulcer patients with intact stomachs, correlated with the duration of symptoms. No decrease is evident with the passage of time.

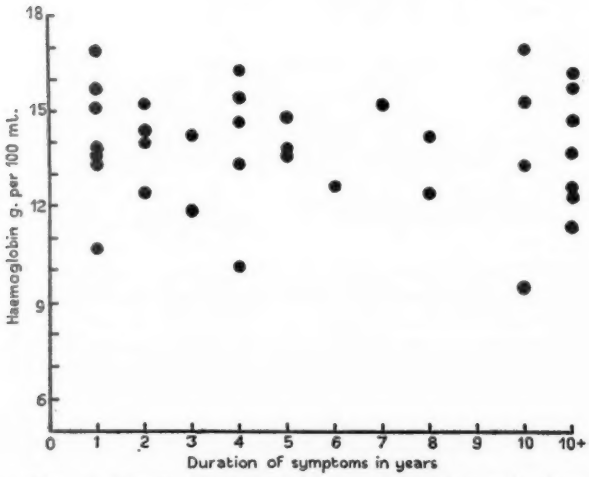


FIG. 7. The haemoglobin levels in 36 female peptic ulcer patients with intact stomachs, correlated with the duration of symptoms. No decrease is evident with the passage of time.

Haemoglobin concentrations, measured in the 127 patients with peptic ulcers but with otherwise intact stomachs, have been plotted in relation to the duration of digestive symptoms (Figs. 6 and 7). In contrast to the patients who had partial gastrectomy, no decline in haemoglobin is evident in either men or

women. Though occasional low values are seen, the time that an ulcer may have been present does not apparently influence the haemoglobin level.

*Nature of anaemia after partial gastrectomy.* The haematological changes suggest iron deficiency as the predominant abnormality, and this is clearly shown in 40 anaemic patients with the lower haemoglobin values (Table III). For purposes of comparison, anaemia has been arbitrarily defined as a haemoglobin

TABLE III

*Mean Haematological Values in Anaemic Men and Women*

| Years after Polya or Billroth gastrectomy | Men | | | | | Women | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Number of cases | Haemoglobin (g./100 ml.) | Red cells (millions/cu. mm.) | Mean corpuscular haemoglobin concentration (per cent.) | Mean corpuscular volume (cu.μ) | Number of cases | Haemoglobin (g./100 ml.) | Red cells (millions/cu. mm.) | Mean corpuscular haemoglobin concentration (per cent.) | Mean corpuscular volume (cu.μ) |
| 0–2 | 5 | 11·2 | 3·9 | 28·0 | 100·0 | 0 | .. | .. | .. | .. |
| 2–4 | 4 | 10·1 | 3·9 | 26·6 | 96·9 | 3 | 7·2 | 3·6 | 24·7 | 83·5 |
| 4–6 | 5 | 9·9 | 3·9 | 26·4 | 94·4 | 5 | 7·0 | 3·6 | 23·3 | 88·5 |
| 6–10 | 10 | 10·2 | 3·9 | 28·0 | 93·0 | 8 | 8·6 | 3·8 | 25·0 | 81·0 |

level in men below 13·3 g. per 100 ml., and in women below 10·4 g. per 100 ml. If 14·8 g. per 100 ml. is taken to represent 100 per cent., these values correspond respectively to 90 per cent, and 70 per cent. In studying the peripheral blood films of the 341 patients who had had a partial gastrectomy, abnormal anisocytosis and poikilocytosis, and microcytosis and hypochromia, were found in 73 cases. A mixed macrocytic and microcytic picture was seen in 31 cases, and occasional macrocytes without microcytes in 10 instances. The findings in the bone-marrow, examined in 20 patients with definite anaemia, corresponded with the peripheral blood picture. The commonest abnormal cell was the micronormoblast, but macronormoblasts were sometimes present. In one patient a megaloblastic anaemia eventually developed. The details are as follows:

*Case 1.* A male patient, aged 62 years in 1956, had a Polya gastrectomy on 15.4.48 for a chronic duodenal ulcer. Free hydrochloric acid was present in the fractional test meal prior to operation. Histological examination showed chronic superficial gastritis, and some follicular lymphocytic infiltration deep in the mucosa. The gastric glands showed no abnormal features. He had a sister with pernicious anaemia. On examination on 10.1.56 he had koilonychia of the right index finger, but no other clinical abnormalities apart from pallor. The haematological investigations showed: haemoglobin, 8·6 g. per 100 ml.; red cells, 3,000,000 per cu. mm.; blood film, microcytic and hypochromic. The bone-marrow showed a normoblastic and macronormoblastic reaction. The fasting serum iron was 80 μg. per 100 ml., and serum vitamin $B_{12}$ 100 μμg. per ml. Liver function tests and a jejunal biopsy showed no abnormality. Tests for faecal occult blood were negative on six occasions. A course of oral ferrous gluconate, 0·3 g. three times daily for three months, produced no improvement, and on 30.5.56 the haemoglobin was 8·6 g. per 100 ml., and red cells 2,000,000 per cu. mm. A further iliac marrow examination showed a megaloblastic reaction. He was given vitamin $B_{12}$, 100 μg. thrice weekly; a maximum reticulocyte response of 15 per cent. was obtained, and a normal blood count was restored. The koilonychia was not evident after treatment for six months with iron and vitamin $B_{12}$.

*Clinical abnormalities associated with anaemia after partial gastrectomy.* The main clinical findings are summarized in Table IV. Koilonychia, transverse nail ridges, and brittle nails, disappeared after iron therapy. Angular stomatitis and atrophic glossitis were also observed, but their improvement after iron therapy was inconstant. Neither bilious vomiting nor diarrhoea was more commonly seen in the anaemic patients.

TABLE IV

*Clinical Abnormalities associated with Anaemia in 341 Post-gastrectomy Patients*

| | *Number of patients* | |
|---|---|---|
| | *Male* | *Female* |
| Koilonychia . . . . . | 3 | 3 |
| Transverse nail ridging . . . . . | .. | 4 |
| Brittle nails . . . . . | 1 | 1 |
| Atrophic glossitis . . . . . | 14 | 22 |

*Alimentary bleeding after gastrectomy.* Occult blood loss in the faeces was investigated by the benzidine test in 30 anaemic and 32 non-anaemic patients after partial gastrectomy. Three hundred and forty-nine determinations of occult blood were made, 157 from anaemic patients and 192 from non-anaemic patients. The incidence of positive reactions in the anaemic group was seven out of 157 determinations (4·5 per cent.), and in the non-anaemic group 12 out of 192 determinations (6 per cent.). These results are to be compared with observations made in 30 peptic ulcer patients who had not undergone operation. They provided 97 specimens of faeces, and positive reactions occurred in seven specimens (7 per cent.) from four patients. Of the non-anaemic patients who had had gastrectomy, four contributed the positive results. The source of bleeding was not detected, and there was no clinical or radiological evidence of recurrent ulcer. Of the anaemic patients, one, who is described below, gave five out of the seven positive results.

*Case 2.* A man aged 70 years had a Polya type of gastrectomy, with removal of four-fifths of the stomach, for a duodenal ulcer, in 1949. The blood count at that time showed no abnormality. He remained moderately well except for gradually increasing lassitude, and when seen again in 1955 he was extremely pale. A blood count confirmed iron-deficiency anaemia: haemoglobin, 8·2 g. per 100 ml.; red cells, 3,400,000 per cu. mm.; and a peripheral blood film showing anisocytosis, poikilocytosis and microcytosis, and hypochromia. The fasting serum iron was 36 $\mu$g. per 100 ml. Marrow examination showed changes compatible with iron deficiency. A barium meal and gastroscopy disclosed no abnormality in the stoma or gastric remnant. Examinations of the faeces for occult blood, however, were consistently positive. On sigmoidoscopy internal haemorrhoids, with superficial proctitis and ulceration, were found, and were assumed to be the source of the bleeding. Ferrous gluconate was given by mouth, and the blood count returned to normal in three months.

*Dietary intake after partial gastrectomy.* The intake of iron, protein, and calories was estimated in patients after partial gastrectomy (Table V). The 40

male patients comprised two equal anaemic and non-anaemic groups. The mean time after operation was similar in the two groups, but the anaemic patients showed a significantly lower intake of iron and protein in the diet ($P < 0.02$). The diets of 40 female patients were also studied, but here the two groups differed with respect to the time interval, as it was not possible to find many women several years after operation who had not developed anaemia. In both groups of women the iron and protein intakes were low, but not significantly different.

TABLE V

*Diet after Partial Gastrectomy*

The mean values and standard errors are shown

| *Clinical group* | *Number of patients* | *Haemoglobin (g./100 ml.)* | *Time after operation (yrs.)* | *Iron (mg./day)* | *Protein (g./day)* | *Total calories/day* |
|---|---|---|---|---|---|---|
| Non-anaemic men . | 20 | 15·1±0·2 | 7·2±0·6 | 15·5±1·2 | 92±3 | 3,059±181 |
| Anaemic men . | 20 | 11·6±0·5 | 7·9±0·6 | 11·5±0·6 | 72±3 | 2,666±138 |
| Non-anaemic women | 20 | 13·5±0·3 | 2·4±0·3 | 8·3±0·5 | 58±3 | 1,953±109 |
| Anaemic women . | 20 | 9·5±0·4 | 5·2±0·5 | 7·3±0·8 | 49±5 | 1,775±145 |

*Haematological response to treatment.* The response to oral therapy with ferrous gluconate was studied in detail in 41 patients who were anaemic after partial gastrectomy. In three patients no response was obtained. In Case 1, already described, there was also vitamin-$B_{12}$ deficiency. The two other patients who failed to benefit from iron by mouth both responded to parenteral iron. The details are as follows:

*Case 3.* A married woman had a Polya partial gastrectomy in 1950, at the age of 40 years, for a chronic prepyloric ulcer. In 1952 she was anaemic (haemoglobin 6·2 g. per 100 ml.; red cells 3,500,000 per cu. mm.), with no history of melaena, and had a course of intravenous iron therapy with great improvement. She again became anaemic in 1955, and received oral iron and ascorbic acid for six months, but little improvement resulted. Her menses were irregular, with heavy losses. On admission the haemoglobin was 5·2 g. per 100 ml. and red cells 2,400,000 per cu. mm., and the blood film and absolute values confirmed severe iron deficiency. Six samples of faeces were negative for occult blood. Estimation of the dietary intake showed an average of 4·6 mg. of iron in the diet per day. There was no clinical evidence of steatorrhoea. The fasting serum iron was 27 $\mu$g. per 100 ml. A course of 1,400 mg. of saccharated oxide of iron was given in divided intravenous injections. A maximum reticulocytosis of 10 per cent. resulted, and the haemoglobin after three weeks was 10·4 g. per 100 ml. This improvement was maintained, and the patient had a normal blood count six months after completing the intravenous iron therapy.

*Case 4.* A married woman aged 35 years had a Polya gastrectomy on 14.2.56 for a chronic duodenal ulcer of 14 years' duration. At that time the haemoglobin was 13·7 g. per 100 ml., and red cells 5,000,000 per cu. mm. She remained well after her operation, apart from repeated bouts of colicky abdominal pains, but had irregular, heavy menstrual bleeding. On 23.11.56 the haemoglobin was 9·8 g. per 100 ml., and red cells 3,700,000 per cu. mm. Ferrous gluconate, 0·3 g., and ascorbic acid, 100 mg., were given three times daily, but the patient had occasional diarrhoea. She persisted, however, with this treatment, and after four months there was little improvement, the haemoglobin being 10·1 g.

per 100 ml. and red cells 3,700,000 per cu. mm. She was then given 1,250 mg. of iron dextran ('imferon') intramuscularly in divided doses, and the haemoglobin level after three months had risen to 13·3 g. per 100 ml. and red cells to 4,300,000 per cu. mm.

The remaining 38 patients all responded to the administration of ferrous gluconate by mouth, though in some cases prolonged treatment was required, together with the simultaneous administration of ascorbic acid. The mean initial haemoglobin in these anaemic patients was 9·6 g. per 100 ml., and after treatment with ferrous gluconate, 1 g. daily, the final mean was 13·6 g. per 100 ml. The mean time taken to achieve this rise was six and a half months, the range being two to 12 months. It is thus apparent that in the majority of patients in whom iron-deficiency anaemia develops after partial gastrectomy a satisfactory response can ultimately be obtained from oral therapy.

## *Discussion*

After partial gastrectomy, anaemia of the iron-deficiency type is commonly found. It has been described in numerous studies (Morley, 1928; Gordon-Taylor, Hudson, Dodds, Warner, and Whitby, 1929; Wells and Welbourn, 1951; Blake and Rechnitzer, 1953; Anderson, Gunn, and Watt, 1955), and has been further confirmed here by examination of the peripheral blood and bone-marrow and the response to treatment with iron. While some macrocytosis is a recognized feature in the blood films of patients examined after partial gastrectomy, the development of megaloblastic anaemia is rare, though it is common after total gastrectomy (Paulson and Harvey, 1954). Only one patient in the present series developed megaloblastic anaemia, but his sister suffered from pernicious anaemia, which is recognized as a familial disease (Callender and Denborough, 1957). This development may accordingly be unrelated to the previous operation.

The gradual decline in the haemoglobin level with the passage of time after partial gastrectomy was a conspicuous feature in all the groups investigated. In the patients with persistent peptic ulceration, but with otherwise intact stomachs, there was no increase in the incidence of anaemia with the duration of time that an ulcer had been present. Furthermore, it seems improbable that a patient with an ulcer producing symptoms is less liable to haemorrhage than a patient who has had a partial gastrectomy and has no evidence of gastric or stomal ulceration. Support for this view was obtained from the investigations of faecal occult blood, as the incidence of positive results was not greater in the partial gastrectomy groups. Nevertheless, bleeding may well be intermittent, and the extent to which alimentary haemorrhage contributes to the fall in haemoglobin levels after partial gastrectomy is difficult to determine. The occasional rapid appearance of anaemia after operation can probably only be attributed to haemorrhage (Paulson and Harvey, 1954; Witts, 1956), though a normal haemoglobin level in a patient with a peptic ulcer before surgery is no indication that the body iron stores are replete. If intermittent occult bleeding

had previously occurred, the iron stores might be partially depleted, and calculation of the amount of iron deficiency required to produce post-gastrectomy anaemia should not be based on the assumption of initial normal iron reserves. The decline in haemoglobin levels observed after operation, and particularly the steep slope in women under 50 years of age, suggest that a patient after partial gastrectomy cannot readily make good any blood loss that may occur. In contrast, the patient who has a peptic ulcer and a complete stomach, though also liable to alimentary haemorrhage, can with the passage of time compensate for any haemorrhage that may have taken place. This is an important and essential difference between the two groups, and shows that additional factors besides haemorrhage are at work in the production of post-gastrectomy anaemia. It is generally accepted that after acute blood loss in normal persons there is a rapid return of the haemoglobin to normal (Cadham, 1938; Fowler and Barer, 1942; Finch, Haskins, and Finch, 1950).

The consumption of an inadequate diet has previously been noted after partial gastrectomy (Hartfall, 1934). In the present work the estimated iron intake can be regarded only as a rough approximation, but nevertheless some differences were revealed. The intake in men anaemic after partial gastrectomy was significantly lower than that found in non-anaemic patients. In the two groups the mean time after operation was similar, and the reduced supply in some men was possibly a factor in hastening the development of anaemia. But a consumption of 11·6 mg. of iron a day is unlikely to lead to anaemia in a man unless some other reason, such as blood loss or malabsorption, is also present. The iron intake of the women was considerably below the 12·0 mg. per day regarded as essential for the prevention of anaemia while menstruation is continuing (National Research Council, 1953). Women who were not regarded as anaemic could be found only in the early period after operation, and it was clear that all eventually became anaemic on this diet. The evidence thus suggests that a reduction of dietary iron after partial gastrectomy is an important factor in the development of anaemia in female patients.

The extent to which malabsorption of iron from the diet after partial gastrectomy may be important in the pathogenesis of anaemia cannot be determined from the present work. In the female patients blood loss from menstruation, and possibly occasional alimentary haemorrhage, coupled with the low intake of iron, may be a sufficient explanation without involving any other factors. In the majority of male patients, however, the iron intake was not reduced to a level regarded as dangerous in health. Nevertheless, they showed after partial gastrectomy a progressive decrease in haemoglobin which was not seen in other male patients with peptic ulcers. In the absence of evidence of an increased liability to bleeding after partial gastrectomy, it seems probable that a reduced ability to absorb iron from the diet may be a contributory factor. This hypothesis has accordingly been made the subject of further investigation.

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*Summary*

A clinical and haematological study has been made of 341 patients after partial gastrectomy for peptic ulcer. A progressive fall in haemoglobin levels was found after both Billroth and Polya types of operation, and in both male and female patients. The steepest fall was seen in women under 50 years of age. The anaemia was predominantly of the iron-deficiency type. Only one case of megaloblastic anaemia was found in this series.

Similar results were not found in patients with peptic ulcers but complete stomachs, when the haemoglobin levels were plotted in relation to the time that ulcer symptoms had been present. There was not a greater incidence of alimentary bleeding, as judged by tests of faecal occult blood, in patients after partial gastrectomy than in other peptic ulcer patients.

The mean dietary iron intake of male patients anaemic after partial gastrectomy was significantly lower than that of non-anaemic male patients, but was not sufficiently low to be the sole cause of the development of the anaemia. In female patients, however, the mean intake of iron in the diet was below the level commonly thought necessary for the maintenance of a normal haemoglobin level.

In the great majority of cases an ultimately satisfactory, but often slow, response was obtained with oral iron therapy.

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# THE PATHOGENESIS OF ANAEMIA AFTER PARTIAL GASTRECTOMY

## II. IRON ABSORPTION AFTER PARTIAL GASTRECTOMY[1]

By I. McLEAN BAIRD and G. M. WILSON

(From the Department of Pharmacology and Therapeutics, University of Sheffield)

The investigation of patients after partial gastrectomy showed that a steady decline in haemoglobin concentration followed the operation (Baird, Blackburn, and Wilson, 1959). Iron deficiency after partial gastrectomy may be attributed in younger women to a combination of haemorrhage and inadequate diet. These factors alone, however, do not account for the fall in haemoglobin levels in men after partial gastrectomy. As iron is principally absorbed from the upper part of the jejunum (Hahn, Bale, Ross, Balfour, and Whipple, 1943; Endicott, Gillman, Brecher, Ness, Clarke, and Adamik, 1949; Stewart, Yuile, Claiborne, Snowman, and Whipple, 1950), and as this region is short-circuited in the Polya operation, there is a theoretical basis for the suggestion that malabsorption of iron is an additional factor (Anderson, Gunn, and Watt, 1955; Capper, 1952). Studies with $^{59}Fe$ given as ferrous sulphate to patients under fasting conditions failed, however, to show any absorption defect resulting from partial gastrectomy (Smith and Mallett, 1957; Baird, Podmore, and Wilson, 1957). It has repeatedly been observed that the iron-deficiency anaemia seen after partial gastrectomy responds to iron preparations given by mouth (Witts, 1956). On the other hand, these experiments with inorganic iron salts do not reproduce the circumstances in which the anaemia developed. Patients after partial gastrectomy must continue to absorb an adequate amount of iron from the diet if they are to maintain a normal haemoglobin concentration. The absorption of organically bound iron taken with food must clearly be investigated in order to determine whether any defect develops. Further, an absorption mechanism which may be adequate for small demands may be unable to expand in response to increased requirements. Iron-deficiency anaemia occurring in patients with an intact stomach provokes, as a compensatory response, an enhanced absorption of iron (Granick, 1951). It is important to determine whether this mechanism is preserved in the patient who has had a partial gastrectomy.

In view of these considerations, observations have been made before and after partial gastrectomy in patients suffering from peptic ulceration. Iron in organic form and labelled with $^{59}Fe$ has been given with meals, and the effect of the operation on iron absorption has been determined. As these patients did not

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show any fall in the haemoglobin level in the few weeks elapsing between the two sets of observations, the studies have been extended to include patients who have become severely anaemic as a result of a partial gastrectomy carried out a few years previously. Their iron absorption has been measured, and the results have been compared with those found in patients who have had no gastric operation but are suffering from iron-deficiency anaemia of a similar degree.

## *Methods*

*Inorganic iron absorption.* The details of the technique have been described previously (Baird, Podmore, and Wilson, 1957). Four microcuries of $^{59}Fe$ of high specific activity were added to a solution containing 0·6 g. $FeSO_4 \cdot 7H_2O$, as described by Badenoch and Callender (1954). This solution ensured that all the $^{59}Fe$ was administered in the ferrous state. Standards for reference were made from this solution, and the radioactivity was determined on a scintillation counter (Ekco N550). A measured quantity of the mixture was given by mouth to the fasting patient, and all the faeces were collected until less than 0·5 per cent. of the dose appeared in the daily collection. Subsequently the faeces were homogenized, and weighed samples were counted for radioactivity. The total excretion of $^{59}Fe$ was then calculated.

*Organic iron absorption.* Rabbits were given intravenous injections of 100$\mu$c. of $^{59}Fe$, which became incorporated in the haemoglobin. After about four days the animals were bled at intervals as required, and the injections were continued so that 1 ml. of the rabbit's blood contained about 1$\mu$c. of $^{59}Fe$. Approximately 4$\mu$c. were used for each test. The requisite amount of blood was added to some distilled water, and the mixture was frozen and thawed to ensure haemolysis, and then centrifuged. Reference standards were prepared from the supernatant fluid, and a measured amount was added to a cup containing 500 mg. of ascorbic acid and a little meat extract (Bovril) for flavouring. This drink was consumed with a meal. In the first series of experiments only a small quantity of food was taken; this consisted of bread (60 g.), butter (15 g.), and marmalade (8 g.). In the second series the drink was taken during the course of a full meal comprising chicken (60 g.), potatoes (30 g.), peas (30 g.), and rice pudding (60 g.). The quantities of food were weighed on each occasion. The patient fasted overnight, and the meal was given between 9 and 10 a.m. All the faeces were collected, and the radioactivity was measured as described above.

*Selection of patients.* The absorption of inorganic iron was studied in patients anaemic as a result of a partial gastrectomy carried out a few years previously. These patients were not troubled with vomiting, diarrhoea, or stomal ulceration, and had not received any treatment with iron. The results in this group are compared with those previously reported in peptic ulcer patients before and shortly after partial gastrectomy (Baird, Podmore, and Wilson, 1957). The absorption of organic iron taken with food was studied more extensively in different groups of patients. Observations were made in patients with peptic ulcers and four to

six weeks after partial gastrectomy, and the effect of the operation was determined in each case with either the small or the large meal. Patients with pyloric stenosis, vomiting, or diarrhoea, and those who required blood transfusions, were excluded. Alkalis, laxatives, and iron therapy were not given during the period of study. The absorption of iron taken in this way was also studied in anaemic patients who had had a partial gastrectomy a few years previously. For comparison, a series of measurements was made in patients with intact stomachs suffering from iron-deficiency anaemia as a result of either acute gastric or duodenal haemorrhage, or repeated blood loss associated with conditions such as menorrhagia or haemorrhoids. The tests were carried out before treatment with iron was given.

### *Results*

*Absorption of inorganic iron.* The results of the investigations carried out on patients anaemic after partial gastrectomy are summarized in Table I. They are compared with the findings in non-anaemic patients with peptic ulcers, before and shortly after partial gastrectomy. Under the conditions of these tests, with the patient fasting and the iron given in the ferrous state, the anaemic patients showed a small but significant decrease in the faecal recovery of $^{59}Fe$ ($P < 0.02$).

TABLE I

*Faecal Recovery of $^{59}Fe$, given under Fasting Conditions as Ferrous Sulphate, in Patients Anaemic after Partial Gastrectomy and in Non-anaemic Peptic Ulcer Patients before and after Partial Gastrectomy*

| | *Number of cases* | *Haemoglobin (g./100 ml.) ±S.E.* | *Faecal recovery of $^{59}Fe$ (% of dose) ±S.E.* |
|---|---|---|---|
| Anaemic after partial gastrectomy . . | 13 | 8·5±0·46 | 76±2·9 |
| Peptic ulcer patients before partial gastrectomy* . . . . . | 16 | 15·5±0·26 | 85±1·8 |
| Same patients three months after partial gastrectomy* . . . . . | 16 | 15·5±0·21 | 84±1·0 |

S.E. = Standard error of the mean.
* Data abstracted from Baird, Podmore, and Wilson (1957)

*Absorption of organic iron taken with food after partial gastrectomy.* Tests of organic iron absorption were carried out before partial gastrectomy in patients suffering from peptic ulceration, receiving either the light or full meal. The observations were repeated four to six weeks after the operation in the same patients under identical conditions (Table II). No change in faecal $^{59}Fe$ recovery was found in the patients receiving the light meal. In those receiving the full meal the faecal recovery of $^{59}Fe$ was increased after partial gastrectomy. There is a wide range between individuals in iron absorption under these conditions, and the means of the observations made with a full meal before and after partial gastrectomy show a difference significant only at the 5 per cent. level. When, however, the results in the individual patients before and after the operation are examined, the mean difference is 6 per cent., and the standard

error of the mean difference is 1·9. This decrease in absorption is highly significant ($P < 0·01$) (Moroney, 1953).

*Absorption of organic iron in anaemic patients.* In 10 anaemic post-gastrectomy patients, given organically bound $^{59}Fe$ with the light meal, there was a

TABLE II

*Faecal Recovery of $^{59}Fe$ given in Organic Form with Light and Full Meals*

| | *Clinical Condition* | *Number of cases* | *Haemoglobin (g./100 ml.) ±S.E.* | *Mean faecal recovery of $^{59}Fe$ (% dose) ±S.E.* |
|---|---|---|---|---|
| Light meal | Peptic ulcer before operation | 15 | 15·1±0·20 | 80±1·3 |
| ,, ,, | Same patients four to six weeks after partial gastrectomy . . . . | 15* | 14·9±0·18 | 81±1·6 |
| ,, ,, | Anaemia two or more years after partial gastrectomy . | 10* | 10·5±0·28 | 75±4·7 |
| Full meal | Peptic ulcer before operation | 25 | 15·6±0·18 | 76±2·1 |
| ,, ,, | Same patients four to six weeks after partial gastrectomy . . . . | 25† | 15·1±0·16 | 82±1·8 |
| ,, ,, | Anaemia two or more years after Polya partial gastrectomy . . . . | 4 | 8·9±0·40 | 86±2·4 |
| ,, ,, | Iron-deficiency anaemia with intact stomach . . | 12 | 9·1±0·55 | 65±4·7 |

* In both these groups two cases were Billroth I operations, the remainder Polya.

† Three cases were Billroth I operations, the remainder Polya.

S.E. = Standard error of the mean.

slight increase in iron absorption in comparison with the pre-gastrectomy patients, but this difference was not significant ($P > 0·2$). Similar observations were made in a further four patients after partial gastrectomy who were given the full meal, and in them, despite the anaemia, there was no augmentation of iron absorption (Table II). For comparison, observations were made using

TABLE III

*Faecal Recovery of $^{59}Fe$ given in Organic Form, Irrespective of Meal Size*

| *Clinical condition* | *Number of patients* | *Hb (g./100 ml.) ±S.E.* | *Faecal recovery of $^{59}Fe$ (% dose) ±S.E.* |
|---|---|---|---|
| Peptic ulcer before operation . . . | 40 | 15·4±0·20 | 78±1·4 |
| Anaemia after partial gastrectomy . . | 14 | 10·0±0·37 | 78±3·5 |
| Anaemia with intact stomach . . . | 12 | 9·1±0·55 | 65±4·7 |

S.E. = Standard error of the mean.

the full meal in 12 patients with intact stomachs, who were suffering from iron-deficiency anaemia. In them the absorption of iron was significantly greater than in the patients similarly studied before partial gastrectomy ($P < 0·05$). Furthermore, the iron absorption in these anaemic patients with intact stomachs was also greater than in post-gastrectomy anaemic patients investigated with the full meal ($P < 0·05$). Unfortunately, the group of post-gastrectomy anaemic patients receiving the full meal was small, and could not readily be increased. But if all the patients receiving organically bound iron are considered together, irrespective of the size of the accompanying meal, the same defect in

absorption is shown, based on larger numbers (Table III). The faecal excretion of $^{59}Fe$ was similar in the non-anaemic peptic ulcer patients before operation and in the anaemic patients after partial gastrectomy. The anaemic patients with intact stomachs absorbed significantly more iron than the non-anaemic peptic ulcer patients before surgery ($P < 0{\cdot}02$) and than the anaemic patients after partial gastrectomy ($P < 0{\cdot}05$). In all the groups of anaemic patients the mean haemoglobin levels were similar, but an augmented iron absorption occurred only in those with intact stomachs.

### *Discussion*

The measurement of iron absorption presents certain difficulties. Less than eight per cent. of dietary iron is absorbed in normal people (Moore and Dubach, 1951), and there are considerable differences between individual subjects (Dubach, Callender, and Moore, 1948). In these circumstances it is difficult to demonstrate any further decrease in absorption that may be brought about by partial gastrectomy. In investigations of this kind it is desirable to ensure that a larger proportion of the dose of $^{59}Fe$ is absorbed in normal subjects. This is partly achieved by maintaining the iron in the ferrous state (Moore, Dubach, Minnich, and Roberts, 1944), and in our tests in patients with complete stomachs about 20 to 25 per cent. of the dose was absorbed. This afforded a greater opportunity of demonstrating any decrease in iron absorption that might be caused by operation on the alimentary tract.

Partial gastrectomy did not impair the absorption of inorganic iron given to fasting patients. The tests were carried out with a large quantity (117 mg.) of iron, but a similar result was obtained with 5 mg. of inorganic iron by Smith and Mallett (1957). The addition of food decreases iron absorption (Mettier and Minot, 1931), and a decrease, after partial gastrectomy, in the absorption of inorganic iron taken with food has recently been reported (Choudhury, Smart, and Thompson, 1957). In the present series no change in the absorption of $^{59}Fe$ in organic form, given with a light meal, was observed after partial gastrectomy, but when it was administered with a full meal a small but significant impairment in absorption was noted. This difference may be associated with the reduction of the capacity of the upper alimentary tract, which leads to more rapid passage into the lower jejunum and ileum, where iron absorption is much less efficient (Endicott, Gillman, Brecher, Ness, Clarke, and Adamik, 1949).

Iron absorption in health is adjusted in accordance with the condition of the iron stores in the body (Granick, 1951). A deficiency leads to an enhanced absorption of iron, and this is clearly a mechanism of great importance in the prevention of the development of iron-deficiency anaemias. The patients with iron-deficiency anaemia following partial gastrectomy showed a slight increase in the absorption of inorganic iron given under fasting conditions. This increase, however, was not as great as might have been anticipated from experience of this dose of iron in anaemic patients with intact stomachs (Smith, 1957), but it is in keeping with the rather slow response to oral iron noted in our treatment

of the anaemia following partial gastrectomy. The defective response to anaemia was more clearly demonstrated when $^{59}Fe$ was administered in organic form along with food. Under these conditions an increased absorption of iron was still seen in anaemic patients with intact stomachs. After partial gastrectomy, however, little or no augmentation was observed. A similar finding has been recently reported in a single patient (Chodos, Ross, Apt, Pollycove, and Halkett, 1957). A loss of the ability to augment iron absorption in response to requirements is clearly an important factor in the progressive development of anaemia after partial gastrectomy.

### *Conclusions as to the Pathogenesis of Post-gastrectomy Anaemia*

The characteristic feature of the anaemia is the progressive decline in haemoglobin concentration, owing to iron deficiency, with the passage of time after the partial gastrectomy. This is seen in all the groups studied, but the fall is steepest in menstruating women. Alimentary blood loss may occur after the operation, but haemorrhage is no more frequent in patients who have had partial gastrectomy than in peptic ulcer patients with complete stomachs; yet the latter do not show a progressive decline in haemoglobin values in relation to the time that an ulcer has been present. Other factors besides loss of blood are clearly at work. The intake of iron in the diet may be inadequate in menstruating women after partial gastrectomy, and this alone may lead to the development of anaemia. In other groups of patients, however, the intake is not sufficiently low to account by itself for the onset of anaemia. The operation of partial gastrectomy leads to a slight decrease in the absorption of organic iron taken with food. This decrease is not consistently associated with any structural changes in the jejunum (Baird and Dodge, 1957). Probably more important is the limitation imposed by the operation on the ability to increase absorption of iron from the diet in response to need. Thus a patient after partial gastrectomy is unable to rely on this physiological mechanism to counteract the effects of blood loss and inadequate diet, and the resultant iron deficiency leads to the progressive fall in haemoglobin levels.

We should like to thank the staff of the United Sheffield Hospitals and Wharncliffe Hospital, Sheffield, who kindly allowed us to study patients under their care, and the Endowment Fund for a grant towards the purchase of $^{59}Fe$. The work was done during the tenure by one of the authors (I.M.B.) of a Leverhulme Fellowship of the Royal College of Physicians and a Ciba Fellowship in the University of Sheffield.

### *Summary*

The effect of partial gastrectomy on the absorption of iron has been investigated under various conditions by the use of radioactive iron preparations.

The absorption of $^{59}Fe$, given as ferrous sulphate with the patient fasting,

was not altered by partial gastrectomy. The absorption of $^{59}Fe$ incorporated in rabbit's blood, and given with a light meal, was also not affected by the operation. When, however, $^{59}Fe$ prepared in this way was given with a full meal, a significant decrease in absorption occurred after partial gastrectomy.

Patients anaemic after partial gastrectomy, given inorganic $^{59}Fe$ while fasting, showed a slightly enhanced absorption, but when the iron was given in organic combination with food there was no increase in absorption. Patients with intact stomachs and iron-deficiency anaemia showed an enhanced absorption when iron was given in this way.

The pathogenesis of iron-deficiency anaemia after partial gastrectomy is reviewed. Haemorrhage and defective diet may be contributory factors, especially in younger women, but a defect in absorption of organic iron taken with food, and particularly an inability to increase iron absorption from the diet in response to need, are of fundamental importance in the causation of the progressive decrease in haemoglobin levels that follows partial gastrectomy.

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# HEPATIC JAUNDICE[1]

By R. G. SHORTER, A. PATON, and J. L. PINNIGER

(From St. Thomas's Hospital and Medical School, London)

With Plates 5 to 10

It is found in the clinical assessment of patients with jaundice that a small group of cases emerges in which the diagnosis is in doubt. Difficulties usually arise because 'obstructive jaundice' can result from both extrahepatic and intrahepatic causes (Eppinger, 1937). Although the majority of patients with acute viral hepatitis pass through a stage in which obstructive features predominate, it is now clear that a small proportion develop prolonged jaundice of an obstructive nature which persists throughout the course of the disease. This is the group to which Watson and Hoffbauer (1946) have applied the term 'cholangiolitic hepatitis'. The diagnostic problem is further complicated by the fact that certain drugs may also cause jaundice of an obstructive type. Of these, methyltestosterone (Almaden and Ross, 1954), arsphenamine (Hanger and Gutman, 1940), and chlorpromazine (Loftus, Huizenga, Stauffer, Rome, and Cain, 1955; Lindsay and Skahen, 1956; Werther and Korelitz, 1957) are well-documented examples. In these difficult diagnostic problems the clinician endeavours to obtain help from biochemical investigations, but it is well known that they often fail to assist in the diagnosis, and this is not surprising, since such tests are largely non-specific. In addition, radiological examinations are notoriously unsatisfactory in the presence of jaundice.

It is generally considered that liver biopsy is of little diagnostic value in the majority of such cases. Weisbrod, Schiff, Gall, Cleveland, and Berman (1950), for example, stated that the differentiation of extrahepatic from intrahepatic obstruction provided the greatest occasion of error in the histological interpretation of liver biopsy material. Popper and Schaffner (1957) agreed that the early stages of hepatitis might be difficult to distinguish histologically from extrahepatic obstruction, and Sborov and Keller (1951) emphasized the fact that some patients might require surgical exploration for the establishment of the diagnosis. In contrast, Gall and Braunstein (1955), in a study of 14 patients suffering from viral hepatitis with obstructive features, concluded that it was possible to distinguish this group histologically with reasonable accuracy from cases of extrahepatic obstruction. Because of this diagnostic difficulty, and the lack of unanimity in the literature, 59 patients with jaundice who were admitted to St. Thomas's Hospital in the period 1952 to 1957 have been studied. It must

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be stressed that they represent a highly selected group of cases. The series was chosen because of clinical, biochemical, and histological discrepancies found when reviewing, in retrospect, 229 consecutive liver biopsies. The following analysis refers to patients in whom a retrospective diagnosis was made as a result of all the information available after a careful follow-up. The first section is devoted to a review of the clinical and biochemical features of these cases. The histological changes are then described, and subsequently the features which are considered to be of diagnostic importance are discussed. It is hoped to show that, where the clinical diagnosis remains in doubt after careful consideration of the biochemical investigations, liver biopsy is of great value in the majority of cases.

## *Clinical Features*

### *Extrahepatic biliary obstruction (extrahepatic cholestasis)*

*Carcinoma.* Thirteen patients had extrahepatic obstruction due to carcinoma involving the biliary system. The site of the obstruction was the head of the pancreas in four cases, the ampulla of Vater in three, the common hepatic duct in three, the gall-bladder, invading the common hepatic duct, in two, and the

TABLE I

*Liver-Function Tests in 13 Patients with Carcinomatous Extrahepatic Biliary Obstruction*

| *Patient* | *Site of obstruction* | *Serum bilirubin (mg./100 ml.)* | *Serum alkaline phosphatase (King–Armstrong units)* | *Thymol turbidity (units)* | *Serum albumin (g./100 ml.)* |
|---|---|---|---|---|---|
| | (Normal) | < 1 | < 15 | 0–4 | 4–4·5 |
| M. P. | Ampulla | 10·4 | 7·5 | 1 | 2·8 |
| E. B. | Pancreas | 5·0 | 16·5 | 1 | 4·3 |
| *E. C. | Pancreas | 9·6 → 15·2 | 18 → 38 | 1 | 3·3 |
| J. H. | Hepatic duct | 12·9 | 18·5 | 3 | 3·8 |
| *M. R. | Gall-bladder → hepatic duct | 11·6 → 25·3 | 20 → 26 | 5 | 5·1 |
| W. N. | Ampulla | 11 → 12 | 21 → 25·5 | 2 → 3 | 4·0 |
| E. E. | Bile duct | 12·0 | 21·8 | 1 | 4·5 |
| T. E. | Hepatic duct | 15·8 | 28 | 1 | 3·8 |
| *W. T. | Ampulla | 1·5 | 30 | 2 | 3·9 |
| E. S. | Hepatic duct | 21 → 25 | 38 | 1 | 3·8 |
| F. E. | Pancreas | 25·2 | 69·5 | 1 | 3·6 |
| L. L. | Pancreas | 13·3 → 15·8 | 82·5 → 24 | 1 | 3·9 |
| G. R. | Gall-bladder → hepatic duct | 37·0 | 95 | 1 | .. |

* Patients with abnormal protein patterns on filter-paper electrophoresis suggesting parenchymatous liver damage.

common bile duct in one case. The single constant clinical feature was jaundice, which had been present for three to six weeks only; in five patients the jaundice had fluctuated in intensity. Abdominal pain, dyspeptic symptoms, and interference with general well-being were uncommon. Pruritus occurred in approximately half the patients and, when present, was severe. Marked enlargement of the liver was found in all cases, and in two the spleen was moderately enlarged. These two patients also had attacks of fever, shivering, abdominal pain, and jaundice, such attacks being generally ascribed to 'cholangitis'. Table I shows that the biochemical findings, in particular the serum alkaline phosphatase, were often at variance with the changes classically thought to accompany

extrahepatic biliary obstruction. Only four patients initially had a serum alkaline phosphatase level of more than 30 King–Armstrong units, and in one of these the level fell below 30 units during the period of observation. Serum albumin was more than 3·5 g. per 100 ml. in all except two patients, thus indicating adequate liver-cell function. Filter-paper electrophoresis of the serum, however, revealed abnormal globulins, suggesting parenchymatous damage, in three instances. Thymol turbidity was normal in 12 of the 13 cases.

*Gall-stones.* Fifteen patients, five of them men, were found to have stones in the extrahepatic biliary system. Intermittent symptoms had been present for from six months to 15 years before the correct diagnosis was made. An

TABLE II

*Liver-Function Tests in 15 Patients with Gall-stones*

| *Patient* | | *Serum bilirubin (mg./100 ml.)* | *Serum alkaline phosphatase (King–Armstrong units)* | *Thymol turbidity (units)* | *Serum albumin (g./100 ml.)* |
|---|---|---|---|---|---|
| | (Normal) | < 1 | < 15 | 0–4 | 4–4·5 |
| K. A. | Female | 3·2 | 20·5 | 1 | 3·2 |
| W. C. | ,, | 1·6 | 10·5 | 1 | 2·2 |
| J. D. | Male | 4·0 | 9·3 | 1 | 2·7 |
| E. H. | ,, | 3·0 | 12 | 8 | 5·2 |
| F. H. | Female | 4·2 | 31 | 1 | .. |
| J. I. | ,, | 2·4 | 22 | 8 | 4·4 |
| C. K. | ,, | 2·4 | 6·5 | 8 | 4·6 |
| G. L. | ,, | 5·2 | 25 → 90 | 2 | 4·0 |
| N. P. | ,, | 1·5 | 33·5 | 1 | 3·8 |
| C. R. | Male | 7·3 | 40 | 4 | 4·6 |
| N. R. | Female | 2·5 | .. | .. | 4·7 |
| E. S. | ,, | 2·5 | 17 | 1 | 3·2 |
| K. S. | ,, | 3·0 | 101 | 2 | 3·7 |
| A. W. | Male | 2·9 | 9·5 | 2 | 5·2 |
| V. W. | ,, | 3·0 | 4 | 1 | 5·6 |

operation on the biliary system had been carried out previously in five cases. In six patients intermittent jaundice, with little or no abdominal pain, had led to a variety of diagnoses. In the remaining nine the clinical features of 'cholangitis' were present. Itching was noted in only two patients, but in many cases no mention was made in the case records of the presence or absence of this symptom. The spleen was moderately enlarged in four of the 15 patients, and this finding had contributed to a diagnosis of portal cirrhosis.

The serum bilirubin ranged from 1·5 to 7·3 mg. per 100 ml. in this group: in all but two cases it was less than 5 mg. per 100 ml. (Table II). The serum alkaline phosphatase was less than 20 King–Armstrong units in seven patients, between 20 and 40 units in five, 90 and 101 units respectively in two, and not recorded in one patient. Thymol turbidity was positive (eight units) in three patients, none of whom had splenomegaly. In spite of prolonged ill-health, the plasma proteins were normal in all but two patients, who had low levels of albumin. No qualitative abnormalities were noted on paper electrophoresis. Sulphobromophthalein-sodium retention was abnormal in the three patients who were tested (10 to 20 per cent. retention after 30 minutes).

Cholecystography revealed stones in only one case. In addition, stones were demonstrated in three patients after the acute attack had subsided; they had not been revealed by previous investigation. Intravenous cholangiography

showed stones in only two of the nine patients in whom this investigation was carried out. Finally, it was in this group that the initial histological interpretation of liver biopsy material was most often uncertain, thus adding to the clinical difficulties.

*Stricture of the common bile duct.* Three women were eventually diagnosed as suffering from post-operative stricture of the common bile duct. The history in each case was that of intermittent attacks of jaundice accompanied by severe abdominal pain, fever, and vomiting, and the difficulty was to establish the cause of these symptoms at operation. One patient underwent three laparotomies before a stricture high up in the common bile duct was finally identified. Splenomegaly was present in two cases, and all the patients were markedly jaundiced (serum bilirubin 6·1, 12·5, and 17·3 mg. per 100 ml.). The serum alkaline phosphatase was more than 40 King–Armstrong units in two patients, and normal in the third. Thymol turbidity and plasma proteins were normal in all three cases.

*Intrahepatic jaundice*

As might be expected from the nature of the present series, there were no cases of classical, uncomplicated viral hepatitis. The 28 patients in this group were submitted to liver biopsy because of atypical presenting features (most frequently those of primary obstruction), or because they were thought to be suffering from one of the rarer causes of jaundice, for example 'primary biliary cirrhosis'.

*Acute intrahepatic cholestasis* (*'cholangiolitic hepatitis'*). This term is used to include patients in whom prolonged obstructive jaundice is thought to be due to the same agent as that causing infective hepatitis. We prefer the term 'acute intrahepatic cholestasis' (Popper and Schaffner, 1952) to 'cholangiolitic hepatitis' (Watson and Hoffbauer, 1946), since the site and mechanism of the jaundice have not yet been elucidated. There were five patients in this group, and they presented great diagnostic difficulty. Jaundice had been present for six to eight weeks when the patients were first seen, and was accompanied by vague ill-health, dyspeptic symptoms, and abdominal pain. Pruritus was a well-marked feature, being present in four cases. In addition to being jaundiced, the patients appeared ill, with evidence of loss of weight. 'Spider' naevi were present in two, but there were no other clinical features which indicated parenchymatous damage.

The serum bilirubin exceeded 10 mg. per 100 ml. in four patients. The serum alkaline phosphatase was normal in three, and between 30 and 40 King–Armstrong units in the other two. Thymol turbidity was normal in two patients, and increased in three. The plasma proteins were quantitatively normal, but electrophoresis revealed abnormalities in two cases: in one there was a band between the $\alpha$- and $\beta$-globulin suggestive of myelomatosis, and in the other an increase in $\gamma$-globulin. Because of the depth of jaundice, no help in differential diagnosis could be obtained from radiological examination of the biliary system.

Four patients were submitted to exploratory laparotomy because of lack of

confidence that aspiration biopsy would assist in the diagnosis. No obstruction to the extrahepatic biliary system was demonstrated by either operative or post-operative cholangiograms. One patient died two weeks after operation as a result of hepatic failure, and another succumbed some months later, while still jaundiced, to bleeding from a duodenal ulcer. In the other three cases the jaundice gradually subsided, and the patients have remained well for one, two, and three and a half years respectively after the original attack.

*Chronic primary intrahepatic cholestasis.* There were two women with a history of long-standing jaundice accompanied by marked pruritus. Clinical examination revealed well-nourished patients, with pigmentation and xanthomata. The biochemical findings were those of obstructive jaundice, with marked hypercholesterolaemia. No extrahepatic obstruction was found at laparotomy. The patients conformed to the excellent description of primary biliary cirrhosis given by Ahrens, Payne, Kunkel, Eisenmenger, and Blondheim (1950). We prefer the term chronic primary intrahepatic cholestasis, however, because we believe that the term 'primary biliary cirrhosis' is more ambiguous.

*Subacute hepatitis.* There were four patients in this group, three women and one young girl. The clinical problem in these patients was the association of a long history of general ill-health with mild jaundice. On examination the patients were well-nourished, often depressed, and had well-marked stigmata of active, severe, parenchymatous liver disease. There was evidence of fluid retention and of disturbed hormonal balance. The outstanding biochemical findings were very high thymol-turbidity levels, ranging from 27 to 54 units, and diminished serum albumin with conspicuously raised globulin concentrations. The height of the thymol-turbidity figures appears to differentiate this group from patients with chronic hepatitis (cirrhosis). The increase of serum globulin was largely confined to the $\gamma$-globulin fraction, and this fact was confirmed by paper electrophoretic studies. The above features appear to be identical with those found in the group of patients recently described by Bearn, Kunkel, and Slater (1956). These authors considered them to represent a syndrome peculiar to young adults with severe parenchymatous liver disease.

*Chronic hepatitis.* Nine patients were finally diagnosed as suffering from chronic hepatitis (cirrhosis). One was found *post mortem* also to have a malignant hepatoma. Features suggesting obstructive jaundice caused considerable confusion in diagnosis. Two patients had short histories of severe pain under the right costal margin, accompanied by vomiting and jaundice. In one of these two there was a strong family history of gall-stones. Three patients showed steadily increasing, though moderate, jaundice, and this was associated with raised serum alkaline phosphatase concentrations. Four patients, including one of the two mentioned above, had concentrations of serum bilirubin ranging from 12 to 23·8 mg. per 100 ml. when first seen. The serum albumin concentrations were below 3 g. per 100 ml. in six cases. In contrast, the thymol-turbidity values were not higher than seven units in any of the patients (Table III).

*Chlorpromazine jaundice.* Four patients were considered to be suffering from intrahepatic cholestasis due to chlorpromazine therapy. Difficulty in diagnosis

arose either because no specific inquiry was made for exposure to the drug, or because the patient was suffering from some other condition, for example carcinomatosis, which might have produced jaundice. There were no specific clinical features that were helpful in reaching the diagnosis. Three patients were submitted to laparotomy without incident. No obstruction was found in the extrahepatic biliary tract, and post-operative cholangiograms were normal. In all four cases the jaundice cleared in from four to six weeks.

TABLE III

*Liver-Function Tests in Nine Patients with Chronic Hepatitis*

| *Patient* | *Serum bilirubin (mg./100 ml.)* | *Serum alkaline phosphatase (King–Armstrong units)* | *Thymol turbidity (units)* | *Serum albumin (g./100 ml.)* |
|---|---|---|---|---|
| (Normal) | < 1 | < 15 | 0–4 | 4–4·5 |
| A. C. | 4·2 | 5·5 | 1 | 4·1 |
| *B. D. | 17·7 | 16 | 1 | 2·5 |
| M. C. | 5·0 | 49·5 | 2 | 4·4 |
| *C. F. | 18·3 | 39 | 3 | 2·7 |
| M. T. | 12·0 | 30 | 3 | 2·3 |
| *M. E. | 1·5 | 12·5 | 6 | 2·8 |
| W. S. | 5·0 | 28 | 7 | 2·0 |
| *W. C. | 4·3 | 35 | 7 | 2·2 |
| S. C. | 23·8 | 12·5 | 7 | 4·1 |

* Patients with increased γ-globulins on filter-paper electrophoresis.

*Miscellaneous.* Of the remaining four patients, three had carcinomatosis with extensive involvement of the liver. The clinical features were those of severe parenchymatous jaundice associated with signs of liver failure. Carcinomatous tissue was revealed in only one case in material from aspiration liver biopsy. In the remaining patient a serum bilirubin concentration of 17·9 mg. per 100 ml., and a serum alkaline phosphatase level of 58 King–Armstrong units, indicated extrahepatic obstruction. At autopsy the liver showed diffuse infiltration by Hodgkin's tissue, and there was no evidence of obstruction to the extrahepatic biliary tract.

### *Histological Features*

Liver biopsy material was obtained both by the percutaneous route and at operation. For routine purposes, however, the former method is recommended, because of the risks of general anaesthesia and exploratory laparotomy in patients with undiagnosed jaundice. Needle biopsy is carried out at St. Thomas's Hospital under local anaesthesia, with a trochar and cannula, after determination of the prothrombin time and the patient's blood group. If necessary, Vitamin K is given beforehand and blood cross-matched as a precautionary measure. A careful watch is kept on the pulse-rate for 12 hours after the procedure. No complications were encountered in the present study. All the liver biopsy material available for study from the 59 cases was fixed in 10 per cent. formalin, and the sections prepared from them were stained with haematoxylin and eosin, haematoxylin and van Gieson, and by silver impregnation for reticulin (A. E. Clark, 1958; personal communication). Staining for bile-pigment by Stein's iodine method was not done as a routine, but was used selectively where necessary. The histological appraisal was made without any

knowledge of the case records, and only after an opinion had been formed was clinical information sought.

*Terminology*

It is necessary first to define the terms used in the ensuing descriptions of the pathological processes, as there is no unanimity of definition in the published reports.

*Liver-cell necrosis.* Two forms are commonly seen. In one, here called eosinophilic necrosis, a pyknotic nuclear change is associated with an alteration in cytoplasmic staining quality. The slightly basophilic and foamy appearance of the normal cytoplasm is replaced by one of a hyaline, eosinophilic nature (Plate 5, Figs. 1 and 2). Infrequently this cytoplasmic change is extreme, and cells may be seen with a very faint outline, containing a roughly circular and deeply eosinophilic body, the cell nucleus having disappeared. Caution must be exercised in the interpretation of the significance of this form of necrosis when it is present along the edge of a section obtained from an aspiration sample which is otherwise normal; in these circumstances the change appears to be a direct result of the technique of biopsy. In the other common type of necrosis the cell outline becomes indistinct, and there is karyolysis of the nucleus. The nuclear degeneration is in advance of that in the cytoplasm. There is no accepted term for this form of necrosis, and it is here called lytic necrosis for brevity (Plate 5, Fig. 1; Plate 7, Fig. 7; Plate 9, Fig. 11). Both types of necrosis may occur in zonal and focal distribution, and may be associated with a variable degree of inflammatory cell response. The latter most commonly consists of mononuclear cells, which are chiefly histiocytes and fibroblasts. Neutrophile leucocytes may predominate (Plate 5, Fig. 3), or may be in approximately equal numbers with the mononuclear cells. Eosinophils and lymphocytes are uncommon.

*Other nuclear changes in liver cells.* It is common to find, in sections of normal liver tissue, variations in the nuclei of liver cells, and occasional binucleate cell forms. In many pathological conditions these changes may be accentuated and, in addition, giant forms of liver cells may be observed. Mitotic figures are never conspicuous. Where focal necrosis is present, these nuclear changes tend to be prominent in cells at the periphery of the necrotic areas. It is considered that these changes are features of liver-cell regeneration. Liver-cell proliferation may be atypical in two situations, at the periphery of the liver lobule or, in the case of cirrhosis, in the neighbourhood of fibrous strands. The new cells may take the form of aggregates bearing a superficial resemblance to bile ductules (Plate 10, Fig. 12). The absence of lumina, and the staining qualities of the nuclei and cytoplasm, indicate an origin from liver cells rather than from bile-ductular epithelium. The term pseudo-ductular proliferation is used in the present study to describe such structures.

*Bile ducts, ductules, and cholangioles.* Two or three biliary channels will be seen in most normal portal tracts. The larger tubes, here called ducts, are lined by tall cuboidal or low columnar epithelium, whereas the small structures, here

called ductules, are lined by low cuboidal epithelial cells. In certain of the diseases to be described dilatation and invagination of the ducts may occur (Plate 8, Fig. 8) and the ductules may increase in number, their histological appearances varying from relatively normal structures (Plate 6, Fig. 4) to bizarre slit-like forms, lined by low cuboidal epithelial cells with hyperchromatic nuclei (Plate 6, Figs. 5*a*, 5*b*), in which it may be impossible to identify any lumen. The terms true and atypical ductular proliferation are used to describe the latter changes. It has not been possible to identify those connecting channels between the liver lobules and the ductules, the so-called cholangioles, which have been presumed to exist by many authors (Eppinger, 1937; Lichtman, 1949).

*Cholestasis.* The term cholestasis is applied to the accumulation of bile pigment within the liver. The pigment is seen within the cytoplasm of hepatic cells as golden-brown globules, and similar accumulations may occur in Kupffer cells. Bile pigment may also be visible in spaces between liver cells as 'bile plugs' (Plate 7, Figs. 6 and 7). These spaces are commonly called 'bile canaliculi', but definite lining membrane cannot be demonstrated in conventional histological preparations or in electron-microscopical studies. The latter show that the boundaries of the spaces are formed by adjacent liver cells (Rouiller, 1954). Necrosis of the cells adjacent to bile plugs may occur, with the formation of 'bile lakes'.

*Extrahepatic biliary obstruction (extrahepatic cholestasis)*

The 31 patients in this group were those with obstructive jaundice due to extrahepatic carcinoma, gall-stones, or simple strictures of the extrahepatic biliary tract. The biopsy material was derived from patients who at the time of biopsy had been jaundiced for at least one week, and this base-line is used for the following chronological descriptions. The changes observed are described collectively, since no significant differences could be attributed to the site or the nature of the obstructing lesion.

1. *Early changes.* The histological features are based on the findings in 14 patients who at the time of biopsy had been jaundiced for periods ranging from one week to one month. The degree of cholestasis varied from case to case, being predominantly centrilobular; mid-zonal cholestasis was seen in two instances. 'Bile lakes' were not observed in this series. Changes in the portal tracts included inflammatory cell reaction, oedema of the connective-tissue framework, fibroblastic activity, dilatation of bile ducts, and proliferation of ductules. The degree of inflammatory cell reaction ranged from negligible to severe. The cell type was variable; in six cases it consisted either entirely of polymorphonuclear leucocytes, or of an admixture of these with mononuclear cells or lymphocytes (Plate 9, Fig. 10); in the remaining eight cases polymorphs were absent, and the inflammatory response was entirely mononuclear. The inflammatory cells extended into the periphery of the liver lobule in 12 cases. No topical relationship between the inflammatory cells and the bile ducts or ductules was observed, nor were polymorphs seen in the bile-duct lumina.

Oedema of the connective tissue of the portal tracts was a constant feature, and was conspicuous in four of the biopsies (Plate 8, Fig. 8). Fibroblastic activity in the tracts was found to be an early feature in all cases, leading to thickening and extension of young fibrous tissue for a short way between the adjacent liver cells (Plate 8, Fig. 9). Assessment of bile-duct dilatation was difficult, but it was clearly present in two of the biopsies. Bile pigment was not seen within the lumina of the ducts or in the lining epithelium. Ductular proliferation was present in five cases, the new ductules being predominantly of normal structure (Plate 6, Fig. 4). Such proliferation, however, was not a conspicuous feature in any of the biopsy material studied. No specific changes were seen in patients suffering from the clinical syndrome of 'cholangitis'. For example, in such cases the incidence of polymorph infiltration of the portal tracts was no greater than in the other examples of extrahepatic biliary obstruction.

Eosinophilic and lytic hepatic cellular necrosis was seen in all cases to a varying degree (Plate 5, Figs. 1 and 2). Lytic necrosis was found especially in relation to central veins, and was severe in eight instances; eosinophilic necrosis was most commonly periportal, both types of necrosis occurring focally as well as in zonal distribution in all the biopsies. No correlation was found between the degree or type of hepatic cellular necrosis and the site or nature of the obstruction. Inflammatory cell reaction to areas of cellular necrosis, either focal or zonal, was slight in 13 cases, and absent in the remaining one. In two of the cases in which the inflammatory cell response in the portal tracts was predominantly polymorphonuclear, the reaction to the areas of necrosis was likewise polymorphonuclear (Plate 5, Fig. 3). In 12 instances, however, the cells in relation to these areas were mononuclear in type, with perhaps an occasional polymorph or lymphocyte. Nuclear variation in liver cells adjacent to the areas of necrosis was seen in all cases. Binucleate forms were increased in number, but were not a prominent feature, and giant liver-cell forms were not observed. Pseudo-ductular proliferation was not a significant finding in any of the biopsies. The reticulin framework of the lobules was normal in all cases.

2. *Later changes.* All the 17 patients in this group had been jaundiced, at the time of biopsy, for periods ranging from one to six months. Hepatic cellular necrosis was present in all cases, was severe in 11, and was predominantly eosinophilic. Cholestasis was observed in all instances. Oedema of the portal tracts was a notable feature in four of the biopsies, but was overshadowed by fibroblastic activity, with the formation of fibrous septa. This increase of fibrous tissue was also seen in the remaining cases. The inflammatory cell response in the portal tracts was variable in degree, the cell type being predominantly mononuclear; in five cases, however, small foci of polymorphs were seen. Inflammatory cell response to the areas of hepatic cellular necrosis was very slight in all instances, and consisted of mononuclear cells. In the regions of the central veins varying degrees of fibroblastic activity were present, and early linkage of these areas of fibrosis with the septa derived from the portal tracts was found in two cases, in which the duration of jaundice was four and six months respectively.

Bile-duct and ductular changes were inconspicuous, and no special topical relationship was seen between these structures and the areas of fibrosis.

*Intrahepatic jaundice*

*Acute intrahepatic cholestasis* (*'cholangiolitic hepatitis'*). Five patients were diagnosed clinically as suffering from acute intrahepatic cholestasis. The duration of jaundice ranged from six to eight weeks at the time of biopsy. The histological features which contrasted with those commonly seen in acute hepatitis (Roholm and Iversen, 1939; Dible, McMichael, and Sherlock, 1943; Mallory, 1947) were the presence of well-marked cholestasis, minimal liver-cell necrosis, and considerable atypical ductular proliferation (Plate 6, Figs. 5*a*, 5*b*).

*Chronic primary intrahepatic cholestasis* had been diagnosed clinically in two patients. The histological picture in the liver biopsy samples showed that the liver architecture was destroyed, and nodular regeneration was present. Cholestasis and abnormal proliferation of bile ductules were also prominent features. This picture, however, was indistinguishable from that seen in two of the cases diagnosed clinically as chronic hepatitis.

*Subacute hepatitis.* In the four cases diagnosed as subacute hepatitis the conspicuous histological features were extensive liver-cell necrosis and an associated mononuclear cell reaction. A variable degree of similar inflammatory cell reaction was present in the portal tracts. Fibroblastic activity extended from the tracts into the surrounding parenchyma, but the reticular architecture of the liver lobule, though damaged, was still preserved. Marked nuclear variation in surviving liver cells, with giant liver-cell formation as a notable feature, was present in all the cases. Pseudo-ductular formations were also seen (Plate 10, Fig. 12). Proliferation of bile ductules was noted in three cases, and was of abnormal form.

*Chronic hepatitis* (*cirrhosis*). In the nine cases clinically diagnosed as chronic hepatitis the reticular framework of the liver lobules was destroyed, and nodules of regeneration were present (Plate 10, Fig. 13). Extensive liver-cell necrosis of both forms, associated with well-marked mononuclear cell reaction, was seen in all the biopsy specimens. Diffuse fibrosis of the liver was a feature common to all cases, and isolated areas of regenerating liver cells within fibrous strands were noted in two. Cholestasis was prominent in four instances, and in five cases markedly abnormal ductular proliferation was present. The latter group included two of the cases in which cholestasis was conspicuous.

*Chlorpromazine jaundice.* The drug chlorpromazine hydrochloride had been associated with diagnostic problems of jaundice in four cases. The duration of jaundice at the time of biopsy ranged from 10 days to one month. Histological diagnosis was made on the observation of cholestasis unaccompanied by any of the other changes which might have been expected in the case of extrahepatic cholestasis or hepatitis. Scanty foci of central and periportal eosinophilic necrosis, and a very slight mononuclear inflammatory cell response in the portal tracts, were the only other features.

*Miscellaneous.* In the biopsy material obtained from three cases in which

carcinomatous metastases were present in the liver, only one showed evidence of carcinoma on histological examination. The changes present in the other two were indistinguishable from those seen in acute viral hepatitis, and similar changes were present in the liver tissue adjacent to the carcinomatous deposit in the first case. The histological appearances in the single case of Hodgkin's disease presented no diagnostic difficulty but, in addition to the infiltration by Hodgkin's tissue, changes were present in the lobules resembling those seen in acute viral hepatitis. In spite of the histological findings, there was nothing clinically in any of the four cases to suggest the presence of viral hepatitis.

### *Discussion*

Few patients with jaundice present any particular problem of diagnosis. One of the results of the present study, however, is the problem presented by patients with lesions of the extrahepatic biliary tract, particularly gall-stones. It was found, for example, contrary to classical descriptions, that the jaundice fluctuated in five patients with carcinomatous involvement of the extrahepatic biliary tract, and two of these patients had moderate splenomegaly. In addition, the occurrence of splenomegaly in four of the 15 patients with gall-stones serves as a reminder that this sign is of little diagnostic help in jaundiced patients. Abdominal pain may be completely absent when there are gall-stones in the bile ducts, in which case the jaundice is liable to be attributed to an attack of acute hepatitis. Similarly, if recurrent episodes of painless jaundice occur, especially if associated with splenomegaly, a diagnosis of subacute hepatitis may be made. On the other hand, particularly in male patients, our series shows that the significance of repeated attacks of fever, pruritus, jaundice, and abdominal pain, resulting from the presence of gall-stones, has been underestimated. This series confirms the fact that radiological investigations frequently fail to reveal the presence of gall-stones. An assessment of the original histological opinions given on the liver biopsies for the whole group of extrahepatic cholestasis shows that cases due to gall-stones were those in which the least assistance was given to the clinician.

A review of the clinical features of the cases of hepatitis included in the present study shows that all forms may be accompanied by symptoms which, *per se*, are usually considered to be features of lesions of the extrahepatic biliary tract. For example, abdominal pain occurs more frequently in chronic hepatitis (cirrhosis) than is generally realized (Ratnoff and Patek, 1942), and may even simulate biliary colic, as in two cases of the present series. The cases of chronic hepatitis also illustrate the fact that operation may be hazardous in this condition, and therefore diagnosis should be made without resort to laparotomy if possible. The operative risk alone appears to justify the use of aspiration liver biopsy in all cases of unexplained jaundice, since the histological diagnosis of hepatitis in aspiration samples presents little difficulty.

Assessment of liver-function tests in the present series confirms the generally held view that such tests are of little value in the diagnosis of jaundice. For

example, the serum-bilirubin concentration may be markedly raised in hepatitis, as well as in extrahepatic cholestasis (Tables I and III). The concentration of serum alkaline phosphatase is also quite unreliable as a diagnostic test. In two-thirds of the patients with lesions of the extrahepatic biliary tract in the present study, the serum alkaline phosphatase was less than 30 King–Armstrong units, the figure which is generally accepted to be the dividing line between intrahepatic and extrahepatic obstruction. This was the major reason for delay in diagnosis in the group of patients with extrahepatic carcinoma. Flocculation tests and changes in the plasma proteins are generally unhelpful, even with the addition of filter-paper electrophoresis, but careful evaluation of the serum-albumin concentration may provide some information, particularly when jaundice is severe. The concentration is well preserved in extrahepatic cholestasis, but tends to fall below 3·5 g. per 100 ml. in chronic hepatitis (Table III). The most sensitive test of liver-cell function, the excretion of the dye sulphobromophthalein sodium, is invalidated by the presence of more than slight degrees of jaundice, and therefore can rarely be applied to the problems of jaundice. It has been said (Johnson and Doenges, 1956) that intravenous corticotrophin will markedly reduce the serum-bilirubin and alkaline-phosphatase concentrations in primary intrahepatic cholestasis, and that this may prove a useful test in diagnosis of this condition from extrahepatic cholestasis. In the only patient in this series in whom this test has been used it was of no diagnostic value, since there was marked improvement in the biochemical features in spite of the fact that a carcinoma of the common hepatic duct was subsequently demonstrated at operation. This finding is in accord with cases reported by other authors (Chalmers, Gill, Jernigan, Svec, Jordan, Waldstein, and Knowlton, 1956; Katz, Ducci, and Alessandri, 1957).

In general, radiological investigations as a diagnostic aid in problems of jaundice are valueless; but, if operation is undertaken and no extrahepatic biliary lesion is found, it is important to obtain direct cholangiograms at the time, since reliance should not be placed on palpation alone.

Liver biopsy has been regarded as unhelpful, largely because intrahepatic and extrahepatic jaundice share common histological features (Weisbrod, Schiff, Gall, Cleveland, and Berman, 1950). This overlapping of histological appearances accounts for the lack of assistance given by the original liver biopsy reports in the cases of extrahepatic cholestasis in the present series. An important result of the present study, however, has been the emergence of certain points of diagnostic difference, and these will now be elaborated. The occurrence and degree of cholestasis in liver biopsy material are unlikely to be of diagnostic value, and this has been the case in the present series. The only condition in which cholestasis, unaccompanied by any other notable changes, was of importance was that of jaundice resulting from exposure to the drug chlorpromazine hydrochloride.

The degree of liver-cell necrosis in the earlier stages of extrahepatic cholestasis has been consistently greater than that found in primary intrahepatic cholestasis of similar duration. This finding is in contrast to the widely held and

unsubstantiated belief that necrosis is unusual in association with extrahepatic obstruction, though Gibson and Robertson (1939) demonstrated that it was a feature of this condition. This necrosis parallels that observed after excision or ligation of the common bile duct in animals (Cameron and Oakley, 1932; Cameron, Griffiths, and Muzaffar Hasan, 1957; Jaques and McAdams, 1957). Inflammatory cell response, however, even to small areas of hepatic cellular necrosis, has been a more constant and prominent feature of hepatitis than of extrahepatic obstruction. Even when the necrosis was extensive in the latter condition, the inflammatory cell response was negligible. Mononuclear cells were the most common cell type in both processes. Polymorphs occurred in addition in both, but when they were the only cells seen extrahepatic biliary obstruction was present.

TABLE IV

*Summary of Points of Histological Difference between Early Extrahepatic Obstruction, Early Primary Intrahepatic Cholestasis (Cholangiolitic Hepatitis), and Chlorpromazine Jaundice*

| *Observed histological features* | *Early extrahepatic obstruction* | *Early primary intrahepatic cholestasis* | *Chlorpromazine jaundice* |
|---|---|---|---|
| Cholestasis | + | + | + |
| Degree of liver-cell necrosis | ++ | + | ± |
| Degree of inflammatory cell reaction to areas of liver-cell necrosis | ± | + | − |
| Predominantly polymorphonuclear response to areas of liver-cell necrosis | S | − | − |
| Polymorph predominance in inflammatory cell reaction in portal tracts | S | − | − |
| Oedema in portal tracts | S | − | − |
| Fibroblastic activity in portal tracts | S | − | − |
| Bile-duct dilatation | S | − | − |
| Typical bile-ductular proliferation | S | − | − |
| Atypical bile-ductular proliferation | − | S | − |
| Variation in liver-cell nuclei | − | S | − |
| Giant liver-cell forms | − | S | − |
| Pseudo-ductular formation | − | S | − |

S = Point of diagnostic significance.

A predominance of neutrophile polymorphs in the cellular reaction in the portal tracts has been found to be strong evidence of extrahepatic cholestasis (Plate 9, Fig. 10). It has not necessarily indicated a complicating infection. A response consisting of mononuclear cells, with or without lymphocytes, neutrophils, and eosinophils, is of no diagnostic value. Assessment of the degree of inflammatory cell response is of no help in the acute phases of the jaundice. In the subacute or chronic stages, however, the presence of an intense mononuclear reaction is in favour of a hepatitic origin. Oedema and early fibroblastic proliferation in the portal tracts, in the early stages of jaundice, have been found to be important features in the diagnosis of extrahepatic cholestasis (Plate 8, Figs. 8 and 9). Dilatation of bile ducts has rarely been observed in this series, and only in association with extrahepatic lesions. Bile-ductular proliferation has been seen in some cases both of hepatitis and of extrahepatic

obstruction. In the former the proliferation was atypical (Plate 6, Figs. 5*a* and 5*b*), whereas in the latter the ductules appeared more normal (Plate 6, Fig. 4).

In the early stages of both hepatitis and extrahepatic obstruction variation in the size of liver-cell nuclei and binucleate cells has been seen. When these changes have been prominent they have been due to hepatitis. The presence of giant liver-cell forms also favours this diagnosis. Regeneration, in the form of pseudo-ductular structures, has been observed in all stages of hepatitis, but in extrahepatic cholestasis it is an uncommon finding. The nodular form of regeneration seen in chronic hepatitis has not been found in the present series in association with chronic extrahepatic cholestasis.

TABLE V

*Points of Histological Difference between Late Extrahepatic Obstruction and Chronic Hepatitis associated with Cholestasis*

| *Histological feature* | *Late extrahepatic obstruction* | *Late hepatitis with cholestasis* |
|---|---|---|
| Cholestasis . . . . | + | + |
| Prominent inflammatory cell reaction . . . . | — | S |
| Atypical bile-ductular proliferation . . . . . | — | S |
| Pseudo-ductular formation . | — | S |
| Regenerative nodule formation prominent . . . . | — | S |

S = Point of diagnostic significance.

Fibroblastic activity has not been found to be a feature of the early stages of hepatitis. In extrahepatic cholestasis, on the other hand, fibroblastic activity in the portal tracts was an early feature (Plate 8, Fig. 9). This change is considered to be of special value in diagnosis.

The main histological features which serve to distinguish between extrahepatic and intrahepatic cholestasis are summarized in Tables IV and V. The extent of any one abnormality has been somewhat sharply defined for the sake of clarity. If these points are assessed and added together in any individual case, a correct diagnosis of the underlying disease can be made with reasonable accuracy. It is for this reason that we consider liver biopsy to be of great value in all patients with jaundice in whom the diagnosis is uncertain, since it can facilitate the early diagnosis of extrahepatic cholestasis, and prevent unnecessary surgical exploration of patients with intrahepatic cholestasis.

The fact that so many clinical, biochemical, and histological features are common to intrahepatic and extrahepatic cholestasis prompts us to suggest that they arise as a result of a common pathological process in the liver. While it is generally appreciated that infective hepatitis may mimic extrahepatic cholestasis, it is not so widely appreciated that the converse is also true. Thus, if a unitary view is accepted, the concept of 'hepatitis' might be applied, with justification, to extrahepatic cholestasis as well as to those conditions for which it is commonly reserved. For the same reason 'chronic hepatitis' is a better

term than 'cirrhosis', because it represents a logical extension of this concept. The adoption of such a single viewpoint, in place of an arbitrary distinction between extrahepatic and intrahepatic cholestasis, might do much to resolve many of the clinical and histological difficulties.

Our thanks are due to the physicians and surgeons of St. Thomas's Hospital for granting us access to the records of patients under their care. Particularly we wish to thank Dr. J. S. Richardson and Dr. H. J. Anderson for their encouragement and interest. We wish to acknowledge the help given us by Mr. A. E. Clark with the photomicrographs. The expenses of the investigation were partly borne by the Endowment Fund, St. Thomas's Hospital.

*Summary*

1. The clinical, biochemical, and histological features of 59 patients with jaundice, selected because of diagnostic difficulties, have been studied.

2. Patients having gall-stones formed the largest group in this series.

3. Biochemical and radiological investigations have been found to be generally unhelpful in diagnosis. This was particularly noticeable with the serum alkaline phosphatase concentration in cases of extrahepatic cholestasis.

4. A study of the histological features of aspiration liver biopsy material from our patients has emphasized the value of this procedure in the differentiation of extrahepatic from intrahepatic cholestasis. The individual abnormalities may be slight, but in summation achieve diagnostic significance.

5. Because of the overlapping of so many of the features of extrahepatic and intrahepatic cholestasis, a unitary concept of 'hepatitis' is proposed.

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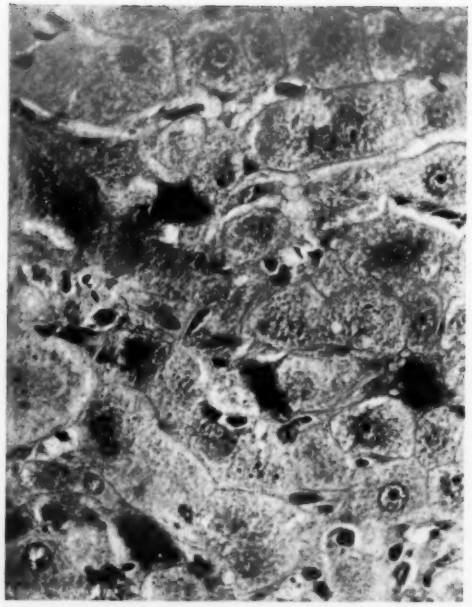

FIG. 1. Eosinophilic and lytic necrosis of liver cells. The former are the darker cells with pyknotic nuclei; the nuclei of the latter show varying degrees of karyolysis (haematoxylin and eosin, ×450)

FIG. 2. Centrilobular eosinophilic necrosis (haematoxylin and eosin, ×450)

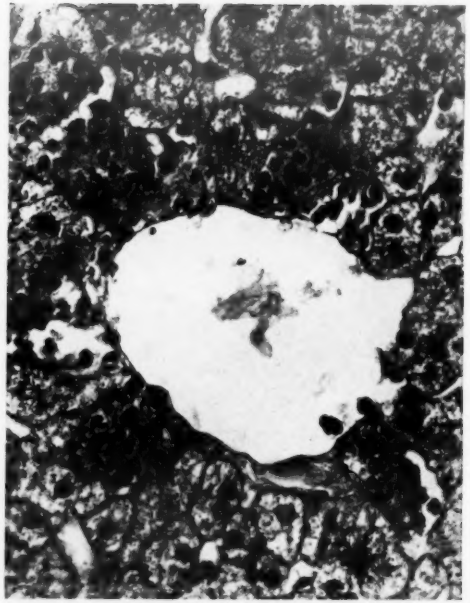

FIG. 3. Centrilobular lytic necrosis, associated in many instances with polymorph infiltration (haematoxylin and eosin, ×450)

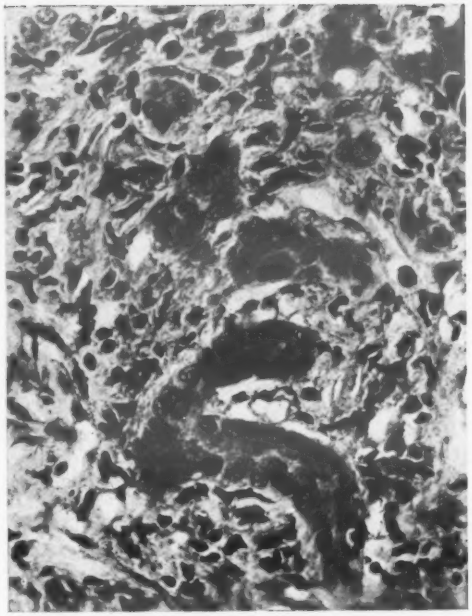

FIG. 4. Portal tract showing true ductular proliferation and increase of mononuclear cells (haematoxylin and eosin, ×450)

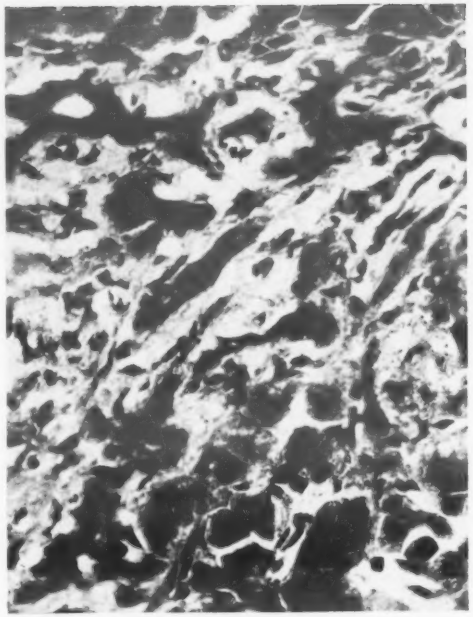

FIG. 5a. Portal tract showing atypical ductular proliferation (haematoxylin and eosin, ×450)

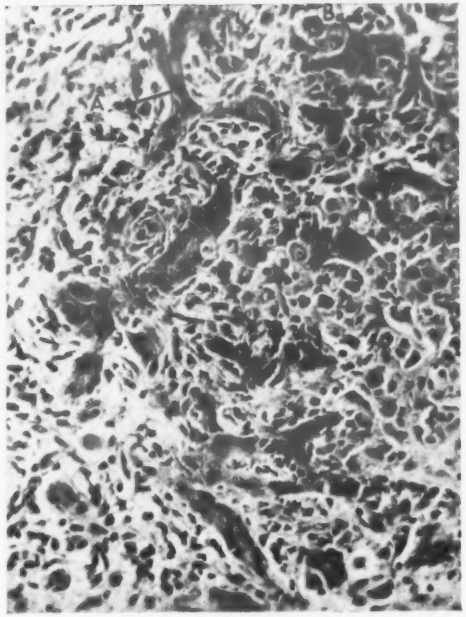


FIG. 5b. Portal tract showing atypical ductular proliferation (A), with slight pseudo-ductular formation (B) and a predominantly mononuclear cellular infiltration (haematoxylin and eosin, ×233)

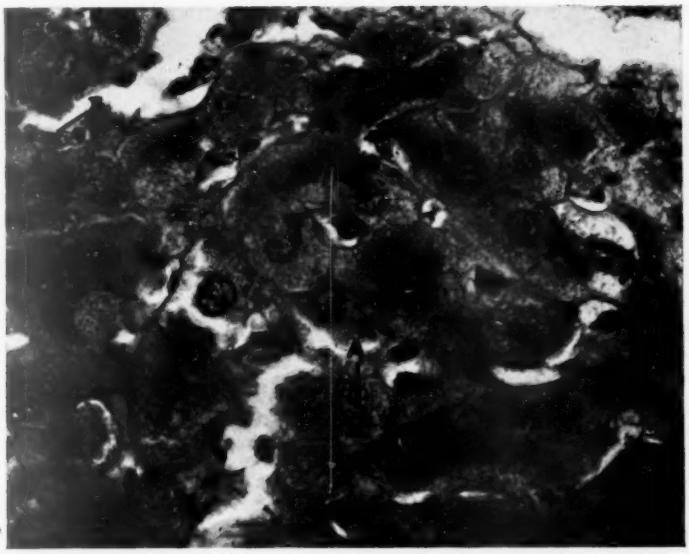

FIG. 6. Cholestasis. Bile plugs are prominent, and pigment granules can also be seen within liver cells (A) and Kupffer cells (B) (haematoxylin and eosin, × 540)

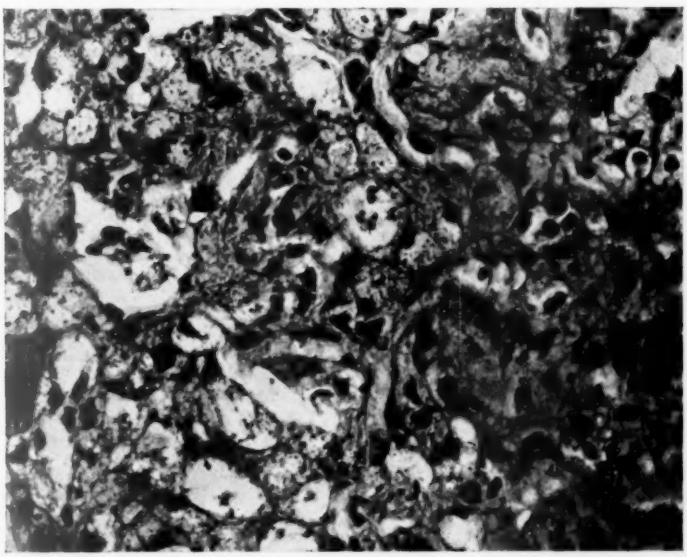

FIG. 7. Lytic necrosis of liver cells, which also contain bile-pigment granules (haematoxylin and eosin, × 540)

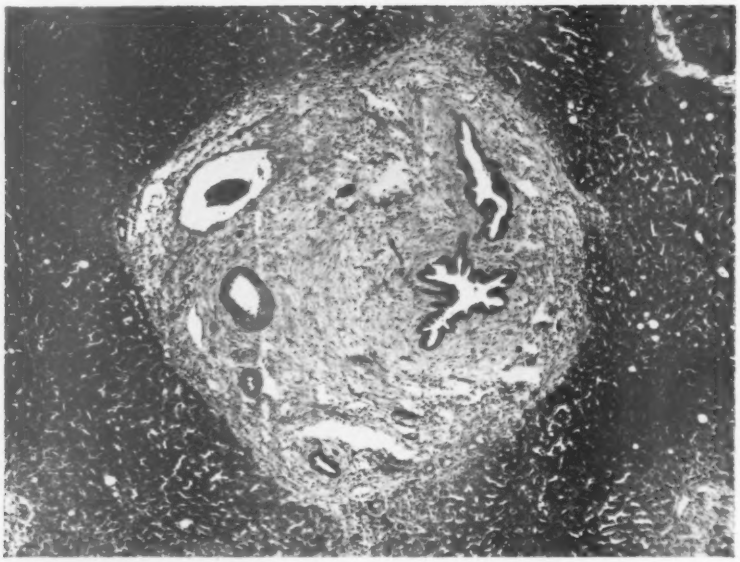

FIG. 8. Portal tract in extrahepatic biliary obstruction, showing oedema and hyperplasia of the epithelium of the bile ducts (haematoxylin and eosin, ×40)

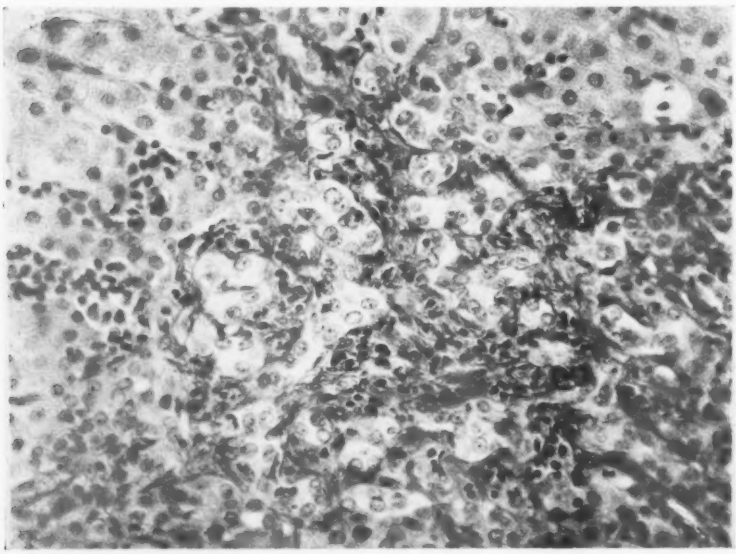

FIG. 9. Extrahepatic biliary obstruction. Fibroblastic proliferation, early true ductular proliferation, and mixed inflammatory cell infiltration in a small portal tract (haematoxylin and van Gieson, ×280)

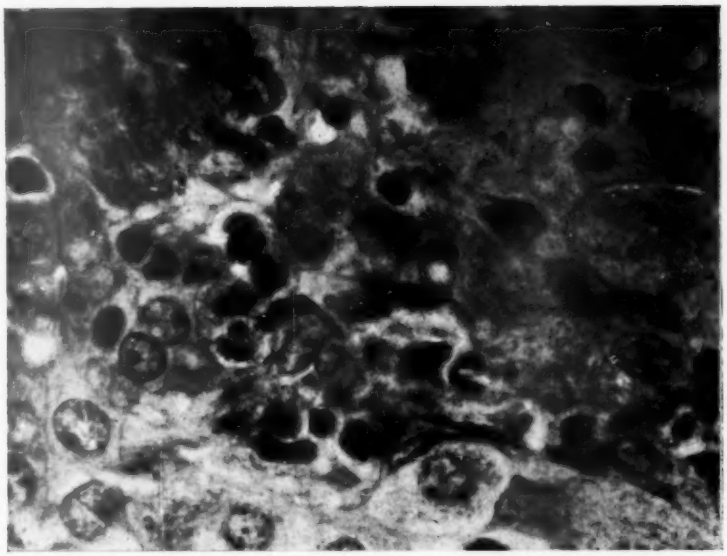

FIG. 10. Extrahepatic biliary obstruction. Portal tract showing predominantly polymorphonuclear inflammatory cell infiltration. Many of the cells out of focus are of this type (haematoxylin and eosin, × 1,000)

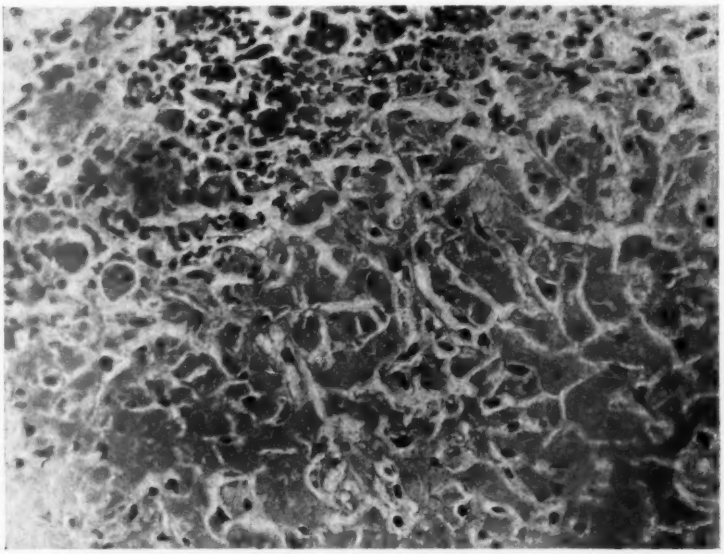

FIG. 11. Extrahepatic biliary obstruction. Extreme lytic necrosis of liver cells (haematoxylin and eosin, × 280)

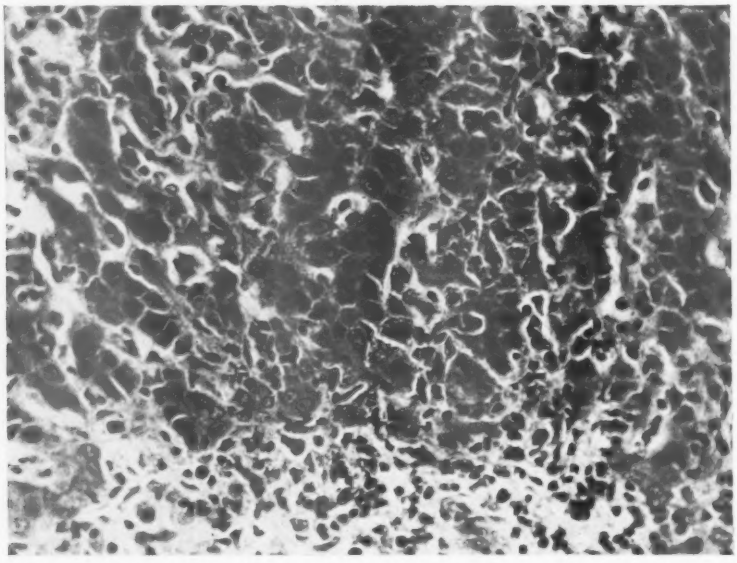

FIG. 12. Hepatitis. Portal tract showing pseudo-ductular proliferation in adjacent liver cells (haematoxylin and eosin, ×280)

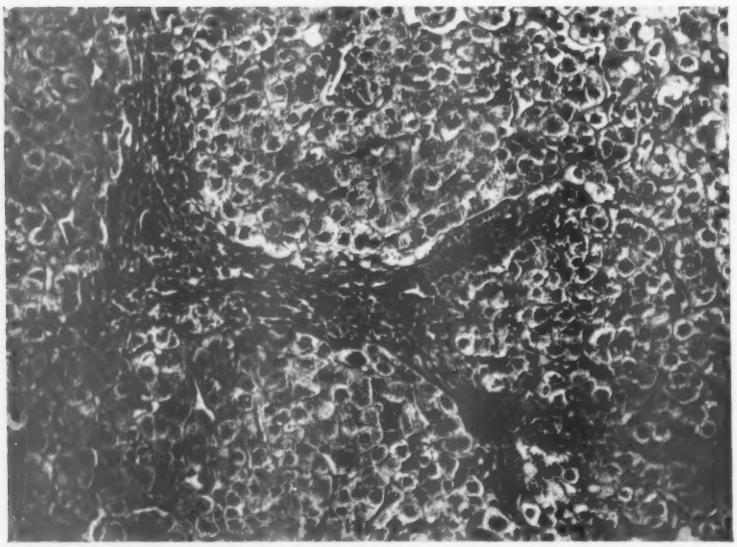

FIG. 13. Chronic hepatitis. Nodular regeneration of liver cells. Fibrosis, with mononuclear inflammatory cell infiltration of the fibrous strands (haematoxylin and eosin, ×140)

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# PROGESTERONE METABOLISM IN MYASTHENIA GRAVIS[1]

By I. SCHRIRE

(From the Department of Endocrinology, New End Hospital, London)

MYASTHENIA GRAVIS is an uncommon disease, yet there is an incidence of at least one in 40,000 of the population. Garland and Clark (1956) have recorded that in Britain alone there are probably about 2,000 sufferers. The mechanisms concerned in the production of myasthenia gravis are imperfectly understood. Whether the endocrine system has a role in its causation has been the subject of dispute, but there is not much doubt that the thymus gland is in some way intimately involved. Although the claims of the thymus for inclusion in the endocrine system have been suspect, its relationship to myasthenia gravis has been firmly established. It is well-known that tumours of the thymus are frequently discovered in affected persons. Even a simple enlargement of the gland, without the presence of a tumour, has been shown to have an undoubted association with myasthenia gravis.

Blalock, Harvey, Ford, and Lilienthal (1941) were among the first to remove the thymus in patients suffering from myasthenia gravis, and they reported a measure of success. Keynes and Carson (1942) confirmed these results, and since then thymectomy has been repeatedly performed. Collins (1946) and Bratton (1948) demonstrated characteristic alterations in the histology of thymus glands removed from myasthenic patients. Today thymectomy appears to have a legitimate place in the treatment of myasthenia gravis, since it may not only alleviate the symptoms and signs but may, in a number of patients, abolish the disease. This has been found to be true in patients with tumours of the thymus, and also in those with a simple enlargement of the gland. Although natural remissions are believed to be common, making the assessment of results difficult, there is little doubt that in some cases thymectomy cures myasthenia gravis. A satisfactory explanation of these findings has not yet been suggested, and it is still not possible to foretell with confidence the results of thymectomy in any one patient.

Certain facts are known concerning the possible relationship between myasthenia gravis and the endocrine system. Marine (1928) noted that in pregnancy the thymus often underwent a process of involution. It has also been long recognized that during pregnancy the severity of the symptoms in myasthenia gravis are modified, and in certain phases of the menses the symptoms are seen to change. Viets, Schwab, and Bazier (1942) investigated the relationship of pregnancy to myasthenia gravis, and reported that pregnant patients might

[1] Received March 14, 1958.

have remissions more complete than any experienced in the natural course of the disease. Fraser and Turner (1953) stated that there was a tendency for the disease to relapse in the first three months of pregnancy, although the patients subsequently regained strength and came safely and well to parturition. Schlezinger (1955) agreed that there might be a tendency to worsening of the disease in the first trimester, followed by a partial or even complete remission in the last few months. This amelioration of symptoms in the last few months of pregnancy has often been confirmed. Schlezinger noted that in the early post-partum period relapses were likely to occur. He also reported that improvement is not always seen in the last few months of pregnancy, some patients, indeed, suffering from relapses during any part of its course. Adams (1946) described alterations in the symptoms in myasthenic patients during the varying phases of the menses, and this is a not uncommon finding in clinics devoted to the study of myasthenia gravis.

The relation of myasthenia gravis to pregnancy and menstruation suggests an association between the thymus gland and the endocrine system. Endocrine changes in pregnancy and at the menses may be profound, and gross variations are seen in the production and excretion of the gonadotrophins, oestrogens and progesterone. Oestrogens are excreted in increasing amounts from the third month of pregnancy, until a maximum is attained in the last month. Pregnanediol, an end product of progesterone metabolism, increases in the fourth month of pregnancy, and reaches very high levels in the blood and urine at parturition. A few days after parturition pregnanediol excretion drops almost to nil. There is thus an apparent association between the amelioration of symptoms in pregnant myasthenic patients and alterations in the production of these hormones. Variations also occur in their production at different phases of the menses, and may be associated with modifications of the myasthenic state.

There is increasing evidence that the thymus gland exerts some degree of influence on endocrine glands, and also that the thymus may itself have an endocrine function. Comsa (1957) described transitory stimulation of the adrenal glands in guinea-pigs after thymectomy, as measured by changes in the weight and ascorbic-acid content of these glands. Weaver (1955) showed that rats after adrenalectomy developed hypertrophy of the thymus gland, and that injections of corticotrophin caused a loss of weight in the thymus. The recent development of new biochemical methods has enhanced the reliability of published data claiming that the thymus has an internal secretion.

Since variations in the production of oestrogens and progesterone are encountered with alterations in adrenal function, and during pregnancy and the menstrual cycle, and since the symptoms of myasthenia gravis are ostensibly linked with phases of pregnancy and the menses, it was decided to investigate the role, if any, that the thymus plays in the metabolism of these hormones in myasthenia gravis. It was decided in the first instance to study the metabolism of progesterone. The pioneer work of Sir Geoffrey Keynes (1949) at the New End Hospital has led to the reception there of many patients suffering from myasthenia gravis, and thymectomy is regularly performed in cases

considered suitable for operation. The present paper records a study of the effects of thymectomy on the metabolism of progesterone in patients with myasthenia gravis.

### *Methods and Material*

The determination of progesterone is still a very difficult and inaccurate procedure, since progesterone is present in amounts which are barely detectable by bio-assay methods. Pregnanediol, however, an end product of progesterone metabolism, is present in the urine in quantities which can be estimated accurately by chemical methods. It is generally agreed that the estimation of

TABLE I

*Urinary Pregnanediol: Normal Levels*

Klopper, Michie, and Brown (1955)

| *Sex* | *Range (mg./24 hrs.)* | *Average (mg./24 hrs.)* |
|---|---|---|
| Male | 0·38–1·42 | 0·92 |
| Female proliferative phase | 0·78–1·5 | 1·12 |
| Female luteal phase | 2·1–4·2 | 3·3 |
| Female post-menopausal | 0·28–0·86 | 0·63 |

urinary pregnanediol has proved most useful in gauging the rate of progesterone elaboration and metabolism (Pearlman, 1952), and no better method is at present practicable. The chemical methods used in the past for the determination of urinary pregnanediol have been inaccurate and unreliable, and their inadequacy has been reflected in the published results. Recently a sensitive and precise chemical method has been developed by Klopper, Michie, and Brown (1955). This method has been used in the present study. Table I summarizes Klopper, Michie, and Brown's findings in normal male subjects, and in normal female subjects in different phases of the menses and in the post-menopausal state. Their method is today generally accepted, and the results have been satisfactorily confirmed.

To check and further evaluate alterations in the functions of the adrenal glands, the urinary 17-hydroxicorticoids have been measured on many occasions in the present study. The method used was that of Appleby, Gibson, Norymberski, and Stubbs (1955). Collections of the 24-hour urine were periodically checked for completeness by measuring the daily creatinine excretion according to the method of Folin (1914).

### *Patients Investigated*

Forty-nine patients suffering from myasthenia gravis have been studied. Ten were investigated both before and after thymectomy; 16 were investigated only before thymectomy; 23 were investigated only after operation. Normal subjects were studied to confirm the findings of Klopper, Michie, and Brown (1955), and to compare their responses with those of the myasthenic patients

after injections of progesterone and corticotrophin. These subjects were hospital patients known not to be suffering from any endocrine disease; patients who had undergone operation for non-toxic nodular goitre were also included. Most of the subjects studied after thymectomy were out-patients, although several of them were admitted to hospital for investigation. Urine specimens were collected in special bottles, and detailed instructions were given for the

TABLE II

*Classification of Grades of Severity in Myasthenia Gravis*

Schrire (1957)

| *Symptoms* | *Grade* |
|---|---|
| No disability | 0 |
| Normal activity, slight ocular weakness | 1 |
| Grade 1 plus involvement of face and pharynx | 2 |
| Grade 2 plus weakness of upper limbs | 3 |
| Grade 3 plus weakness of lower limbs and trunk | 4 |
| Generalized weakness; barely ambulant | 5 |

complete collection of 24-hour urine. The patients collected all the urine passed, and the complete amounts were brought to the hospital. The periodical checks on the accuracy of the collections by means of creatinine determinations showed that there was a very high degree of co-operation. The patients investigated in hospital were under rigid supervision, and their urine collections were also checked by creatinine determinations. The clinical state of each patient was recorded on many occasions. A simple method for comparing the clinical state of a patient at various times has been published (Schrire, 1957), and Table II shows the scheme adopted for this purpose.

## *Results*

### I. *Pregnanediol excretion*

*Fourteen normal subjects* have been investigated. Each was studied for at least 10 successive days. Nine were men, and five were women; two of the latter were post-menopausal. The results are shown in Table III. Two of the women were studied for more than a month. As female subjects excrete different amounts of pregnanediol during the proliferative and the luteal phases of the menstrual cycle, the luteal levels in those patients still menstruating normally and regularly were also recorded. The results in normal patients agree well with those obtained by Klopper, Michie, and Brown (1955) (Table I).

*Myasthenic patients before thymectomy.* Sixteen patients were studied. The results are shown in Table IV. Ten of these 16 patients were subsequently subjected to thymectomy, and the later results are recorded in Table V. Thirteen were women and three were men. Two of the former were post-menopausal. The figures for the luteal phase, shown in parentheses in the Table, represent the maximum amounts of pregnanediol in the urine, in a single 24-hour period, at that phase. The degree of severity of the disease is indicated (see Table II). The urinary 17-hydroxicorticoid levels are recorded for some of

the patients, but were not estimated in all cases; the results in those examined were all within the limits of normal. In all patients in this group, with the

TABLE III

*Urinary Pregnanediol in Normal Subjects*

| *Subject* | *Sex* | *Pregnanediol in urine (mg./24 hrs.)* | | |
|---|---|---|---|---|
| | | *Maximum* | *Minimum* | *Average* |
| 1 | M | 1·31 | 0·68 | 1·2 |
| 2 | M | 1·22 | 0·5 | 0·95 |
| 3 | M | 1·3 | 0·85 | 1·1 |
| 4 | M | 1·4 | 0·78 | 1·0 |
| 5 | M | 1·26 | 0·76 | 0·84 |
| 6 | M | 1·32 | 0·68 | 1·12 |
| 7 | M | 1·2 | 0·54 | 0·75 |
| 8 | M | 1·06 | 0·69 | 0·85 |
| 9 | M | 1·5 | 0·76 | 1·15 |
| 10 | F | 1·46 | 0·84 | 0·25 (P.P.)<br>3·95 (L.P.) |
| 11 | F | 0·84 | 0·52 | 0·69 Post-menopausal |
| 12 | F | 1·04 | 0·42 | 0·83 Post-menopausal |
| 13 | F | 1·56 | 0·84 | 1·14 (P.P.) |
| 14 | F | 1·48 | 0·72 | 1·3 (P.P.)<br>3·86 (L.P.) |

P.P. = proliferative phase.
L.P. = luteal phase.

TABLE IV

*Urinary Pregnanediol in Myasthenia Gravis*

| *Patient* | *Sex* | *Age (years)* | *Myasthenia gravis* | | *Urinary pregnanediol (mg./24 hrs.)* | | | *17-hydroxi-corticoids (average) (mg./24 hrs.)* |
|---|---|---|---|---|---|---|---|---|
| | | | *Duration (years)* | *Grade* | *Maximum* | *Minimum* | *Average* | |
| 1 | M | 38 | 5 | 4 | 0·52 | 0·34 | 0·45 | .. |
| 2 | M | 45 | ½ | 3 | 0·62 | 0·36 | 0·4 | 9·6 |
| 3 | M | 40 | 3 | 3 | 0·6 | 0·3 | 0·49 | 8·8 |
| 4 | F | 42 | 1 | 2 | 0·48 | 0·38 | 0·43 (P.P.) (1·31 L.P.) | .. |
| 5 | F | 22 | 1½ | 3 | 0·72 | 0·4 | 0·42 (P.P.) (1·3 L.P.) | .. |
| 6 | F | 24 | 1 | 4 | 0·66 | 0·42 | 0·5 (Amenorrhoea) | .. |
| 7 | F | 27 | 1¼ | 3 | 0·52 | 0·32 | 0·45 (P.P.) (1·32 L.P.) | 5·6 |
| 8 | F | 9 | 1½ | 2 | 0·68 | 0·38 | 0·52 (P.P.) | .. |
| 9 | F | 36 | 7 | 2 | 0·7 | 0·34 | 0·42 (P.P.) (2·2 L.P.) | 5·1 |
| 10 | F | 31 | 13 | 2 | 0·54 | 0·38 | 0·39 (P.P.) (1·25 L.P.) | 10·2 |
| 11 | F | 30 | 4 | 2 | 0·48 | 0·4 | 0·46 (P.P.) (1·1 L.P.) | 11·9 |
| 12 | F | 45 | 20 | 2 | 0·56 | 0·4 | 0·48 (Post-menopausal) | 8·9 |
| 13 | F | 27 | 14 | 3 | 0·68 | 0·36 | 0·46 (P.P.) | 7·8 |
| 14 | F | 28 | 3 | 2 | 0·72 | 0·32 | 0·48 (P.P.) (1·8 L.P.) | 4·5 |
| 15 | F | 35 | 9 | 2 | 0·48 | 0·36 | 0·35 (P.P.) (1·4 L.P.) | 10·2 |
| 16 | F | 51 | 10 | 1 | 0·84 | 0·56 | 0·72 (Post-menopausal) | 3·5 |

P.P. = proliferative phase.
L.P. = luteal phase.

exception of one who was in a state of complete remission, the urinary pregnanediol level was at the lowest limit of normal or well below it. All the patients were studied for a minimum of 10 successive days, and some daily for several weeks. The luteal rise in the female patients still regularly menstruating was well below the lowest luteal limit of normal, except in Patient 9, who attained this lowest level of normal excretion.

*Myasthenic patients studied before and after thymectomy.* Ten patients were studied both before and after thymectomy. The results are presented in Table V. Two were male and eight were female. With the exception of one woman who had amenorrhoea, and one child, the female patients had regular and normal menstrual histories. Six of the 10 patients were later followed up at varying intervals; four could not be examined again. The shortest follow-up period was

TABLE V

*Urinary Pregnanediol Before and After Thymectomy*

| | | | *Myasthenia gravis* | | *Urinary pregnanediol (mg./24 hrs.)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *Before thymectomy* | | | *After thymectomy* | | | | |
| *Patient* | *Sex* | *Age* | *Duration (years)* | *Grade* | *Maximum* | *Minimum* | *Average* | *7 days* | *14 days* | *21 days* | *28 days* | *Follow-up and average excretion (mg./24 hrs.)* |
| 1 | M | 48 | $\frac{1}{2}$ | 3 | 0·62 | 0·36 | 0·4 | 0·4 | 0·75 | 1·65 | .. | 6 months: 2·6 |
| 2 | F | 22 | $1\frac{1}{2}$ | 3 | 0·48 | 0·38 | 0·43 | 0·45 | 0·9 | 1·2 | .. | .. |
| 3 | F | 24 | 1 | 2 | 0·66 | 0·42 | 0·5 | 0·3 | 0·4 | 0·7 | 0·9 | 6 weeks: 1·3<br>14 months: 1·9 |
| 4 | F | 27 | $1\frac{1}{2}$ | 3 | 0·52 | 0·32 | 0·45 | 0·4 | 0·8 | 1·2 | .. | 11 months: 2·6 |
| 5 | F | 9 | $1\frac{1}{2}$ | 3 | 0·56 | 0·39 | 0·55 | 0·75 | 1·0 | 0·95 | .. | .. |
| 6 | M | 40 | 3 | 4 | 0·57 | 0·4 | 0·49 | 0·8 | 0·9 | 1·2 | .. | 3 months: 1·6<br>15 months: 3·9 |
| 7 | F | 36 | 7 | 3 | 0·6 | 0·3 | 0·45 | 0·75 | .. | 1·1 | .. | 4 weeks: 1·6 |
| 8 | F | 31 | 13 | 2 | 0·84 | 0·56 | 0·75 | 0·5 | 1·8 | 1·9 | .. | 6 weeks: 2·2<br>8 weeks: 1·7<br>10 weeks: 2·4 |
| 9 | F | 35 | 9 | 3 | 0·49 | 0·38 | 0·46 | 0·8 | 1·0 | 1·5 | .. | .. |
| 10 | F | 27 | 14 | 3 | 0·48 | 0·36 | 0·35 | 0·65 | 1·2 | 1·35 | .. | .. |

within four weeks of operation, and the longest 15 months. The immediate effects of thymectomy can be seen to have come within about two weeks after operation. In seven patients the urinary pregnanediol had increased to about double the amount found before operation. Three weeks after thymectomy nine of the 10 patients excreted quantities of pregnanediol three to four times as great as the pre-operative amount, and well within the normal levels for their sex. None of the results in the female patients was recorded from the luteal phase. They are thus readily comparable with the previous levels, which were also recorded during the proliferative phases. The follow-up investigation shows further considerable changes. In the six patients studied, the pregnanediol in the urine had increased markedly. The amounts of pregnanediol excretion were from three to nearly eight times the pre-operative levels, and in four patients the levels were well above those found in normal subjects.

Although the excretion of 17-hydroxicorticoids was estimated in five of the patients before and after thymectomy, there was no demonstrable change in the amounts found before and after the operation. The levels varied between 5·5 mg. and 14 mg. in 24 hours. The clinical state of the patients, as expected, was not immediately affected by operation. Some, however, were taking smaller doses of prostigmine within several weeks of thymectomy.

*Myasthenic patients studied only after thymectomy.* The 23 patients studied (Table VI) had undergone operation at various times before this investigation. All but two had been operated on more than two years previously. These two

patients had been studied also before thymectomy but, as more than a year had elapsed after the operation, it was decided to include them in the present group. The female patients were all studied during the proliferative phase of the menses. Thus the quantities of excreted pregnanediol must be regarded as minimum amounts. Five of the female patients were post-menopausal. A number of the patients were studied more than once, some while in hospital. The

TABLE VI

*Urinary Pregnanediol and 17-Hydroxycorticoids in Myasthenic Patients Studied Only After Thymectomy*

The pregnanediol estimations in the female patients were all made in the proliferative phase of the menses. The results are thus the minimum amounts excreted.

| *Patient* | *Sex* | *Age (years)* | *Duration of disease (years)* | *Date of thymectomy* | *Grade of disease* | | *Urinary pregnanediol (average) (mg./24 hrs.)* | *Urinary 17-hydroxi-corticoids (average) (mg./24 hrs.)* |
|---|---|---|---|---|---|---|---|---|
| | | | | | *Before operation* | *After operation* | | |
| 1 | M | 26 | 9 | 1952 | 3 | 2 | 2·2 | .. |
| 2 | F | 46 | 8 | 1950 | 4 | 1 | 2·5 | 10·0 |
| 3 | M | 35 | 6 | 1953 | 3 | 0 | 2·3 | 17·4 |
| 4 | M | 44 | 8 | 1950 | 4 | 2 | 2·8 | 13·6 |
| 5 | F | 22 | 9 | 1952 | 4 | 2 | 1·5 | 7·3 |
| 6 | M | 33 | 9 | 1949 | 3 | 2 | 4·1 | 14·9 |
| 7 | F | 36 | 6 | 1951 | 3 | 2 | 2·8 | 9·4 |
| 8 | F | 44 | 10 | 1950 | 3 | 2 | 4·0 | 13·2 |
| 9 | M | 35 | 10 | 1952 | 3 | 1 | 2·4 | 12·4 |
| 10 | F | 35 | 7 | 1956 | 3 | 2 | 1·4 | .. |
| 11 | M | 37 | 16 | 1942 | 3 | 0 | 2·3 | 10·7 |
| 12 | M | 49 | 16 | 1942 | 3 | 0 | 2·2 | 6·1 |
| 13 | F | 53 | 16 | 1942 | 2 | 0 | 1·9 | .. |
| 14 | F | 48 | 6 | 1955 | 4 | 4 | 1·0 | .. |
| 15 | M | 34 | 7 | 1951 | 3 | 0 | 2·2 | 10·5 |
| 16 | F | 24 | 10 | 1949 | 3 | 2 | 1·2 | 7·3 |
| 17 | M | 33 | 17 | 1942 | 3 | 0 | 2·9 | 11·9 |
| 18 | F | 44 | 19 | 1950 | 4 | 3 | 1·1 | 9·5 |
| 19 | F | 36 | 12 | 1953 | 3 | 2 | 1·2 | .. |
| 20 | F | 55 | 15 | 1955 | 3 | 3 | 1·4 | .. |
| 21 | F | 24 | 1 | 1956 | 5 | 2 | 1·9 | .. |
| 22 | M | 40 | 3 | 1956 | 3 | 2 | 3·9 | 9·8 |
| 23 | F | 44 | 8 | 1952 | 3 | 2 | 1·8 | 10·5 |

majority were not in hospital when they collected urine for the investigation. The results recorded are the average of successive periods of collection of urine varying from two to 20 days. They show that more than two years after thymectomy pregnanediol excretion may be from three to eight times as great as that found in myasthenic patients before operation. The majority of patients excreted pregnanediol in quantities far in excess of normal subjects. The levels of 17-hydroxicorticoid excretion are shown in 16 patients. All the results are well within the limits for normal subjects. The clinical state of each patient before and after thymectomy is also recorded. Six of the 23 patients were cured. They no longer complained of any symptoms, they were not taking prostigmine, and they did not excrete creatine in the urine. They thus satisfied the criteria suggested by Schrire (1957) for assessing a complete clinical cure of the disease.

II. *Progesterone injection*

*Normal subjects.* Six subjects were studied. Progesterone was injected

intramuscularly in doses of 100 mg. or 200 mg., and the individual amounts administered are indicated in Table VII (A). Klopper, Michie, and Brown (1955), and subsequently other observers, have claimed the recovery of injected progesterone, estimated as urinary pregnanediol, to be from 9 per cent. to 15 per cent. The lower level is probably more often encountered. In the present study the recovery of injected progesterone, estimated as pregnanediol, varies from 8·48 per cent. to 10·1 per cent., with an average of 9·25 per cent., agreeing well with the results of other investigators.

TABLE VII

*The Effect of Injection of Progesterone on the Excretion of Pregnanediol in Normal Subjects and in Patients Suffering from Myasthenia Gravis*

| | *Urinary pregnanediol (mg./24 hrs.)* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A. *Normal subjects* | | | | | | B. *Patients with myasthenia gravis* | | | | | |
| *Day* | *1* | *2* | *3* | *4* | *5* | *6* | *1* | *2* | *3* | *4* | *5* | *6* |
| 1 | 1·1 | 0·85 | 1·3 | 0·95 | 1·25 | 0·84 | 0·35 | 0·44 | 0·36 | 0·4 | 0·6 | 0·5 |
| 2 | 0·9 | 0·8 | 1·2 | 1·15 | 1·1 | 0·72 | 0·4 | 0·6 | 0·42 | 0·6 | 0·6 | 0·6 |
| 3 | 0·85 | 0·7 | 0·95 | 1·2 | 1·2 | 0·95 | 0·45 | 0·54 | 0·35 | 0·56 | 0·42 | 0·54 |
| 4 | 1·0 | 1·0 | 1·3 | 1·1 | 0·85 | 1·0 | 0·4 | 0·5 | 0·45 | 0·5 | 0·4 | 0·32 |
| 5 | 0·9 | 0·8 | 1·2 | 0·98 | 1·0 | 0·76 | 0·35 | 0·45 | 1·8* | 0·5 | 0·42 | 0·54 |
| 6 | 7·8† | 2·9* | 8·2† | 3·1* | 8·1† | 2·3* | 1·2* | 2·4* | 1·8 | 2·9* | 2·6† | 3·3† |
| 7 | 6·4 | 3·8 | 6·4 | 3·0 | 8·0 | 2·1 | 2·6 | 1·2 | 1·6 | 2·6 | 2·4 | 3·1 |
| 8 | 5·7 | 3·6 | 5·0 | 3·6 | 5·2 | 2·75 | 1·9 | 1·9 | 0·55 | 1·8 | 2·8 | 1·8 |
| 9 | 3·6 | 1·8 | 4·8 | 2·8 | 3·6 | 2·7 | 0·6 | 1·9 | 0·4 | 1·1 | 2·1 | 1·8 |
| 10 | 1·1 | 0·65 | 1·9 | 1·8 | 1·5 | 1·9 | 0·45 | 0·6 | 0·35 | 0·6 | 0·65 | 1·7 |
| 11 | 0·85 | 0·74 | 0·9 | 0·86 | 0·9 | 0·85 | 0·35 | 0·3 | 0·42 | 0·6 | 0·43 | 0·6 |
| 12 | 0·95 | 0·88 | 1·1 | 0·82 | 0·9 | 0·67 | .. | 0·38 | .. | 0·45 | 0·48 | 0·54 |
| % Recovery | 9·8 | 8·78 | 10·1 | 8·92 | 9·5 | 8·48 | 4·53 | 5·36 | 4·17 | 6·24 | 4·05 | 4·5 |

Intramuscular injection of progesterone: * 100 mg.
† 200 mg.

*Myasthenia gravis before thymectomy.* Six patients were studied. The results are shown in Table VII (B). The recovery of the injected progesterone, estimated as urinary pregnanediol, varies from 4·05 per cent. to 6·24 per cent. with an average excretion of 4·8 per cent.

*Myasthenia gravis before and after thymectomy.* Five patients were studied before and after thymectomy. Two patients could be studied only after thymectomy. Table VIII shows the results obtained. (The results in the first five patients are also recorded in Table VII (B).) Intramuscular injections of progesterone were given from five to 20 days after thymectomy. The amounts injected are shown in the Table, and were similar to those injected before operation. Two patients were followed up and were given injections for a third time, about a year after thymectomy. Within a few days after thymectomy normal conditions are apparently restored, and the amounts of progesterone recovered, estimated as urinary pregnanediol, are as found in normal subjects. In the two patients who received injections a year after the operation, for the second time after thymectomy, the recovery was within the limits for a normal subject. Two patients were studied only after thymectomy. After the injection of progesterone they also excreted pregnanediol in quantities similar to those found in normal subjects.

TABLE VIII

*The Effect of Injection of Progesterone on Pregnanediol Excretion in Myasthenia Gravis Before and After Thymectomy*

*Urinary pregnanediol (mg./24 hrs.)*

| | *Patients* | | | | | | |
|---|---|---|---|---|---|---|---|
| *Day* | *1* | *2* | *3* | *4* | *5* | *6* | *7* |
| 1 | 0·35 | 0·36 | 0·4 | 0·6 | 0·5 | | |
| 2 | 0·4 | 0·42 | 0·6 | 0·6 | 0·6 | | |
| 3 | 0·45 | 0·35 | 0·56 | 0·42 | 0·54 | | |
| 4 | 0·4 | 0·45 | 0·5 | 0·4 | 0·32 | | |
| 5 | 0·35 | 1·8* | 0·5 | 0·42 | 0·54 | | |
| 6 | 1·2* | 1·8 | 2·9* | 2·6† | 3·3† | Not known | Not known |
| 7 | 2·6 | 1·6 | 2·6 | 2·4 | 3·1 | | |
| 8 | 1·9 | 0·55 | 1·8 | 2·8 | 1·8 | | |
| 9 | 0·6 | 0·4 | 1·1 | 2·1 | 1·8 | | |
| 10 | 0·45 | 0·35 | 0·6 | 0·65 | 1·7 | | |
| 11 | 0·35 | 0·42 | 0·6 | 0·43 | 0·6 | | |
| 12 | .. | .. | 0·45 | 0·48 | 0·54 | | |

THYMECTOMY

| Interval after operation → | 5 days | 6 days | 20 days | 7 days | 7 days | 8 years | 1¼ years |
|---|---|---|---|---|---|---|---|
| 1 | 0·6 | 0·45 | 0·7 | 0·8 | 0·4 | 1·1 | 0·9 |
| 2 | 0·5 | 0·55 | 0·6 | 0·52 | 0·6 | 1·3 | 1·2 |
| 3 | 0·7 | 0·55 | 0·7 | 0·65 | 0·4 | 1·0 | 1·1 |
| 4 | 2·4* | 1·9* | 0·6* | 4·4† | 3·9† | 0·85 | 0·9 |
| 5 | 3·8 | 3·5 | 2·9 | 2·9 | 3·9 | 3·4* | 2·7* |
| 6 | 1·6 | 2·6 | 2·85 | 3·8 | 3·5 | 3·0 | 3·6 |
| 7 | 1·8 | 2·2 | 2·75 | 2·8 | 2·6 | 3·8 | 3·1 |
| 8 | 0·6 | 0·9 | 2·8 | 3·2 | 2·6 | 2·2 | 2·8 |
| 9 | 0·4 | 0·8 | 0·9 | 2·6 | 2·1 | 1·8 | 2·4 |
| 10 | .. | .. | 0·6 | 1·6 | 0·82 | 1·7 | 1·1 |
| 11 | .. | .. | .. | 0·8 | 0·52 | 1·6 | 0·85 |
| 12 | .. | .. | .. | .. | .. | 0·9 | 0·86 |

| Interval after operation → | | | 14 months | | 11 months |
|---|---|---|---|---|---|
| 1 | .. | .. | 1·2 | .. | 2·6 |
| 2 | .. | .. | 2·0 | .. | 1·1 |
| 3 | .. | .. | 2·6 | .. | 2·0 |
| 4 | .. | .. | 1·9 | .. | 1·4 |
| 5 | .. | .. | 1·2 | .. | 1·5 |
| 6 | .. | .. | 5·0† | .. | 6·2† |
| 7 | .. | .. | 5·6 | .. | 6·4 |
| 8 | .. | .. | 5·0 | .. | 5·6 |
| 9 | .. | .. | 6·8 | .. | 4·8 |
| 10 | .. | .. | 3·2 | .. | 1·6 |
| 11 | .. | .. | 2·5 | .. | 1·5 |

*Percentage recovery*

| | *1* | *2* | *3* | *4* | *5* | *6* | *7* |
|---|---|---|---|---|---|---|---|
| Before operation | 4·53 | 4·17 | 6·24 | 4·05 | 4·5 | .. | .. |
| After operation | 7·2 | 8·16 | 9·6<br>8·6 | 8·22 | 8·1<br>7·9 | 10·08 | 9·6 |

Intramuscular injection of progesterone: * 100 mg.
† 200 mg.

## Table IX

*The Effect of Injection of Corticotrophin on Pregnanediol Excretion in Normal Subjects*

| | *Urinary pregnanediol (mg./24 hrs.)* Subjects | | | | |
|---|---|---|---|---|---|
| *Day* | *1* | *2* | *3* | *4* | *5* |
| 1 | 1·2 | 0·84 | 0·96 | 0·68 | 1·24 |
| 2 | 1·1 | 0·96 | 0·78 | 0·88 | 1·34 |
| 3 | 0·88 | 0·86 | 1·2 | 0·84 | 1·2 |
| 4 | 1·12 | 1·1 | 1·14 | 0·8 | 1·34 |
| 5 | 3·4* | 4·1* | 5·0* | 0·78 | 5·7* |
| 6 | 5·6 | 6·2 | 4·8 | 4·5* | 4·3 |
| 7 | 4·2 | 4·0 | 2·6 | 4·4 | 2·9 |
| 8 | 2·3 | 1·8 | 1·2 | 4·2 | 2·8 |
| 9 | 1·4 | 1·2 | 0·84 | 1·4 | 1·3 |
| 10 | 0·76 | 0·68 | 1·0 | 0·88 | 1·0 |
| 11 | 0·88 | 0·98 | 0·86 | 0·8 | 1·21 |
| 12 | 0·92 | .. | 0·92 | 1·2 | 1·12 |
| 13 | .. | .. | .. | 1·1 | .. |

* Intramuscular injection of corticotrophin, 80 units.

## Table X

*The Effect of Injection of Corticotrophin on Pregnanediol Excretion in Myasthenic Patients*

(Before thymectomy: three patients. Before and after thymectomy: four patients. After thymectomy only: three patients.)

| | *Urinary pregnanediol (mg./24 hrs.)* Patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Day* | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* |
| 1 | 0·42 | 0·6 | 0·4 | 0·7 | 0·42 | 0·38 | 0·5 | | | |
| 2 | 0·4 | 0·52 | 0·35 | 0·68 | 0·66 | 0·52 | 0·6 | | | |
| 3 | 0·38 | 0·42 | 0·45 | 0·44 | 0·44 | 0·44 | 0·55 | | | |
| 4 | 0·44 | 0·48 | 0·45 | 0·68 | 0·6 | 0·4 | 0·45 | | | |
| 5 | 6·4* | 16·0* | 0·6 | 0·58 | 8·4* | 6·2* | 10·8* | | | |
| 6 | 8·8 | 8·4 | 0·5 | 7·9* | 8·0 | 6·4 | 10·0 | | | |
| 7 | 6·6 | 3·4 | 10·8* | 6·8 | 5·4 | 4·8 | 6·0 | Not known | Not known | Not known |
| 8 | 4·2 | 2·0 | 8·8 | 3·9 | 4·4 | 3·8 | 2·2 | | | |
| 9 | 1·1 | 2·4 | 6·4 | 3·8 | 1·2 | 1·9 | 1·4 | | | |
| 10 | 0·6 | 1·2 | 2·2 | 3·2 | 1·0 | 0·84 | 0·8 | | | |
| 11 | 0·46 | 0·8 | 1·8 | 2·6 | 0·84 | 0·8 | 0·4 | | | |
| 12 | 0·44 | 0·8 | 1·2 | 2·2 | 0·6 | 0·86 | .. | | | |

| | | | | THYMECTOMY | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Interval after operation → | | | | 7 days | 9 days | 8 days | 12 days | 3 years | 6 years | 4 years |
| 1 | .. | .. | .. | 0·7 | 0·6 | 0·64 | 0·7 | 3·2 | 1·2 | 1·5 |
| 2 | .. | .. | .. | 0·6 | 0·46 | 0·82 | 0·6 | 2·8 | 0·9 | 1·55 |
| 3 | .. | .. | .. | 0·8 | 0·74 | 0·68 | 0·6 | 1·8 | 1·24 | 1·4 |
| 4 | .. | .. | .. | 0·6 | 0·64 | 2·8* | 0·72 | 2·0 | 1·22 | 5·9* |
| 5 | .. | .. | .. | 3·8* | 2·8* | 3·2 | 3·2* | 4·6* | 3·9* | 3·8 |
| 6 | .. | .. | .. | 2·8 | 2·4 | 1·4 | 2·6 | 3·2 | 3·4 | 2·6 |
| 7 | .. | .. | .. | 2·6 | 1·8 | 1·6 | 2·0 | 1·2 | 2·8 | 2·2 |
| 8 | .. | .. | .. | 1·4 | 1·2 | 0·88 | 0·8 | 1·5 | 1·8 | 1·4 |
| 9 | .. | .. | .. | 0·8 | 0·7 | 1·2 | 1·1 | 1·0 | 0·8 | 1·5 |
| 10 | .. | .. | .. | 0·68 | 0·62 | 0·64 | 1·0 | 2·1 | 1·6 | 1·46 |

* Intramuscular injection of corticotrophin, 80 units.

III. *The effect of injection of corticotrophin on urinary pregnanediol*

*Normal subjects.* Five subjects were investigated. The results are recorded in Table IX. After injection of corticotrophin urinary pregnanediol increased to a maximum of 6·2 mg. in 24 hours. These results are in agreement with those

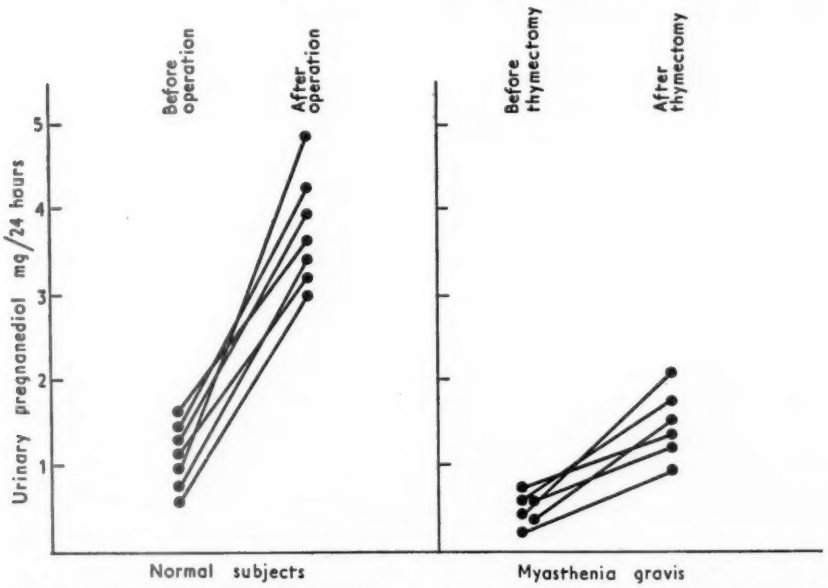


FIG. 1. The effect of surgical operations on the excretion of pregnanediol in normal subjects and in patients suffering from myasthenia gravis. The maximum amount is recorded, and is usually seen within 48 hours after operation. The operation in the myasthenic patients was thymectomy. The pre-operative results recorded are those obtained on the day immediately before the operation.

published by Klopper, Michie, and Brown (1955) and by Nabarro and Moxham (1957) in normal subjects. The excretion of the 17-hydroxicorticoids was also determined after the injection of corticotrophin. The expected increase occurred, and the amounts excreted are in agreement with those obtained by other investigators.

*Myasthenic patients before and after thymectomy.* Three patients received injections only before thymectomy, four both before and after thymectomy, and three only after thymectomy, at least three years after the operation. The results are shown in Table X. After thymectomy the patients responded to the injection of corticotrophin in the same way as normal subjects. The maximum amount of pregnanediol excreted was 5·9 mg. in 24 hours. Before thymectomy, however, the excretion of pregnanediol was markedly increased. Patient No. 2 excreted 16 mg. in one day. The total amount of urinary pregnanediol excreted in response to corticotrophin stimulation, before operation, was far in excess of that found in the normal subjects studied, or in those described by Klopper, Michie, and Brown (1955) and Nabarro and Moxham

(1957). The excretion of the 17-hydroxicorticoids was estimated, and showed the expected increase after injection in all patients, both before and after operation, no difference being found from the response of normal subjects to corticotrophin.

IV. *The effect of surgical operations on pregnanediol excretion in normal subjects and in patients with myasthenia gravis*

Fig. 1 records the results obtained in seven normal subjects and in six myasthenic patients immediately after operation. The normal subjects responded to operation by an increased pregnanediol excretion, and achieved a maximum of 4·8 mg. in 24 hours. These results are in accord with those obtained by Klopper, Michie, and Brown (1955). In patients with myasthenia gravis the increase of urinary pregnanediol after operation did not exceed 2·2 mg. in 24 hours, and the figures shown are well below the levels found in normal subjects.

## *Discussion*

The status of the thymus as an organ of internal secretion has altered considerably in the last few years. It was formerly regarded with little affection by endocrinologists, and the published data regarding its functions have been unsatisfactory and usually contradictory. The impetus given to renewed research was initiated by the fact that in myasthenia gravis the thymus appears to exercise a special effect. The actual role of the thymus in myasthenia is still not clear. There are, nevertheless, indications that it interacts with other endocrine glands, notably the adrenals and the anterior pituitary. In the present investigation evidence is offered that the function of the adrenal glands is probably influenced by an overactive thymus.

The results in Table IV show that pregnanediol excretion in active cases of myasthenia gravis is at the lowest limit of normal, or well below. Not a single patient excreted normal quantities, except one post-menopausal patient, who was in a state of complete remission and was virtually a normal subject. There is always fluctuation in the daily excretion of pregnanediol in normal subjects, and in some the daily amounts excreted varied between 0·75 and 1·65 mg. in 24 hours. The urinary pregnanediol in myasthenic patients appeared to be permanently depressed, variations were slight, and the excretion did not exceed 0·72 mg. in 24 hours. Fig. 2 graphically presents the results obtained in all the cases studied: pregnanediol excretion in the patients with active myasthenia gravis who had not undergone operation is seen to be significantly low.

The increase in the excretion of pregnanediol at the luteal phase of the menses is usually striking. Only two normal female subjects were here studied, and the results are in accord with those of other workers. An enormous amount of work is entailed in this type of study, and it was considered that if two subjects responded in the manner found by other investigators it was sufficient to show that the present results were comparable with such findings. The two normal women excreted increased quantities of pregnanediol at the luteal phase

of the menses (3·95 mg. and 3·86 mg. in 24 hours), according well with the figures published by other observers. Eight of the female myasthenic patients were studied at the luteal phase of the menses as well as during the proliferative phase. The results (Table IV and Fig. 2) show that the excretion in only one patient reached the lowest level observed in normal subjects (2·2 mg. in 24 hours). In five patients the maximum level was less than 1·4 mg. in 24 hours, in one 1·4 mg. in 24 hours, and in one 1·8 mg. in 24 hours.

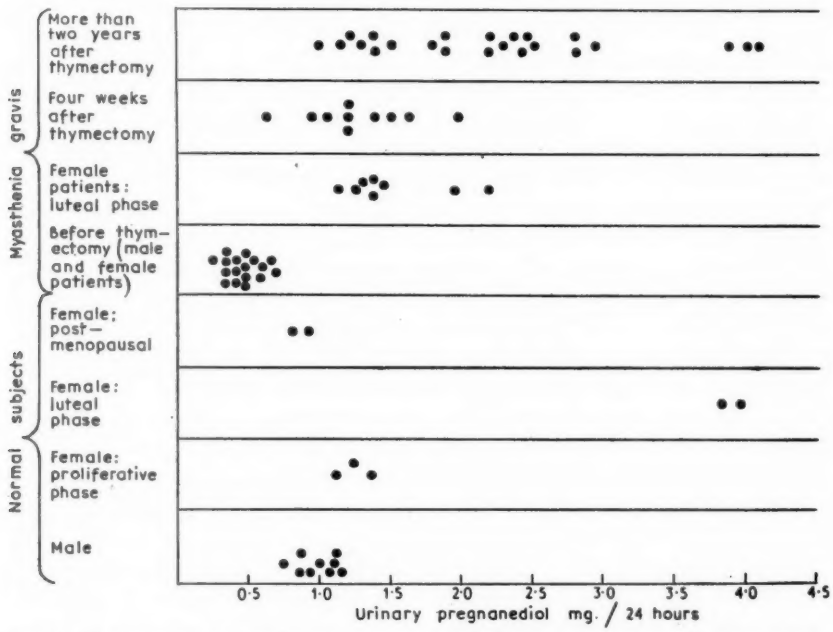


FIG. 2. The excretion of pregnanediol in normal subjects, in patients with myasthenia gravis, and in myasthenic patients before and after thymectomy.

The small excretion of pregnanediol in male patients, in post-menopausal women, and in women during the proliferative phase of the menses, suggests that since progesterone, a precursor of pregnanediol, is presumably derived from the adrenal glands, the adrenals in myasthenic patients must be unable to secrete normal quantities of progesterone. The increased amounts of pregnanediol excreted during the luteal phase are derived from the ovaries. The fact that the quantities excreted in the luteal phase are also well below those found in normal subjects suggests that the adrenals are not alone involved, but that in myasthenia gravis there may also be either a suppression of ovarian function or else a disturbance of the mechanism of conversion of progesterone to pregnanediol. As this conversion is presumed to occur in the liver, it is possible that the liver may be affected in some way in myasthenia gravis. The excretion of the 17-hydroxicorticoids is within normal limits in patients with myasthenia gravis; this fact suggests that either the effect of thymus

over-activity is specific in the control of the production of adrenal progesterone, or the site of thymic influence may be elsewhere, possibly in the liver.

After thymectomy there is no change in the excretion of pregnanediol until about 10 days have elapsed. The level of urinary pregnanediol gradually rises, until within three weeks there is a significant increase. After 14 days seven of the 10 patients studied excreted about twice as much pregnanediol as before operation. At the end of the third week the amounts excreted were three to four times the pre-operative levels. Further observations after a period of six months or more could be made in only four cases. Table V indicates that after thymectomy there is a very great rise in pregnanediol excretion, and levels may be reached which are well above the highest limit in normal subjects. These results suggest that after thymectomy there is not an immediate increase of pregnanediol excretion. Excretion increases within two to three weeks, but this does not preclude the possibility that the thymus in myasthenia gravis exerts a direct inhibitory effect on the adrenal glands, which ceases after thymectomy. The fact that the effect of thymectomy is not immediate also suggests other possibilities, notably that the thymus may exert its effect either on the liver, where progesterone is metabolized to pregnanediol, or on the anterior pituitary, with subsequent alterations in the production of corticotrophin. Whatever the mechanism of this inhibitory effect may be, there is little doubt that after thymectomy there is increased elimination of pregnanediol. Table VI and Fig. 2 show the effects of thymectomy on pregnanediol excretion several years after operation. The results in the 23 patients recorded in Table VI were obtained only after thymectomy. The levels of pregnanediol excretion before operation were not known, and it may be questioned whether they were below the normal limits. In the light of the results obtained in 16 patients before operation (Table IV) it is not unreasonable to suggest that these 23 patients probably also excreted diminished quantities of urinary pregnanediol before thymectomy. After thymectomy, in 13 of these 23 patients the average daily excretion of pregnanediol exceeded 2 mg. Three patients excreted more than 3 mg. in 24 hours, and none eliminated less than 1·0 mg. in 24 hours. None of the female patients in this group was examined in the luteal phase. These results should be compared with the figures shown in Table IV, which show that the 16 patients investigated before thymectomy never excreted more than 0·72 mg. of pregnanediol in 24 hours. It is apparent that after thymectomy some form of inhibitory effect on the excretion of pregnanediol must have been removed. The excretion of the 17-hydroxicorticoids in 16 of the patients is shown in Table VI, and there is no demonstrable abnormality. It is thus possible that the effect of the thymus is specific in the metabolism of progesterone, and does not affect the production of the other adrenal hormones.

It might be inferred that the effect of the thymus in myasthenia gravis is a simple and direct inhibitory effect on the adrenal glands, and possibly on the ovaries at the luteal phase of the menses. The results obtained after the injection of progesterone and corticotrophin make this interpretation difficult to accept. The effect of progesterone injection on pregnanediol excretion differs in normal

subjects and in myasthenic patients. The low level of recovery of progesterone in myasthenic patients before thymectomy is rapidly altered after operation, and returns to within the expected limits of normal. The restoration of normal conditions begins within five or six days after operation, and persists; for in two cases, a year or more after thymectomy, the recovery of injected progesterone was within normal limits. It is not possible to explain this effect by a simple inhibition of the adrenals by thymic secretions. The metabolism of progesterone is presumed to occur in the liver, where it is converted to pregnanediol. Only 10 to 15 per cent. of injected progesterone can normally be accounted for by recovering urinary pregnanediol. The conversion is possibly affected by thymic secretions, either directly or in some manner which is not yet clear. The results of corticotrophin injection do not make the explanation easier.

Five normal subjects, each given intramuscular injections of 80 units of corticotrophin, responded by excreting large quantities of both pregnanediol and 17-hydroxicorticoids. The maximum level of pregnanediol attained after injection was 6·2 mg. in 24 hours. The 17-hydroxicorticoids excreted also reached the levels expected in normal subjects. The injection of corticotrophin into myasthenic patients before thymectomy shows a response which can be explained in at least two ways. It is suggested that the adrenals may be in a hypersensitive state, as found in Cushing's disease (Hubble, 1957), and respond by the excretion of great quantities of pregnanediol. There is also the possibility that the thymus may normally exert an inhibitory effect on the production of corticotrophin by the anterior pituitary. As a result, the injection of corticotrophin would provoke a massive response from a gland previously stimulated to a low degree. The results of injection of corticotrophin into myasthenic patients after thymectomy reveal a return to the normal conditions. There is evidence that the functions of the thymus, the adrenals, and corticotrophin are interrelated. Comsa and Leroux (1955) reported that the thymus has the opposite effect to that of corticotrophin on the adrenals, as it produces a resting phase in these glands, whereas corticotrophin increases adrenal activity. The fact that patients with myasthenia gravis who have had thymectomy respond to corticotrophin injections as do normal subjects certainly suggests that the difference in response by normal subjects and myasthenic patients not operated on is a real one. If these differences are not explicable by interactions of the thymus, the adrenals, and the anterior pituitary, then the site of these different responses to thymectomy, and to injections of progesterone and corticotrophin, may be the liver. No evidence is offered here on the possible role of the liver in these mechanisms. It is obvious that the metabolism of progesterone in liver disease, and the levels of corticotrophin in the blood of normal persons, and of patients with myasthenia gravis before and after thymectomy, will have to be investigated.

This investigation was made during the tenure of a full-time personal grant from the Medical Research Council. I wish to thank Mr. J. Piercey, Sir Geoffrey Keynes, and Dr. Raymond Greene for permission to investigate their patients.

To Dr. R. Bird I am indebted for technical advice. I wish to thank Miss Dorothy Jackson for the estimations of the 17-hydroxicorticoids. I also wish to thank Dr. E. A. Carmichael for allowing me to investigate one of the patients in his care at the National Hospital, Queen Square, and for commenting on the work done.

*Summary*

1. Progesterone metabolism has been studied in 49 patients suffering from myasthenia gravis. Sixteen were studied before thymectomy; 10 were studied both before and after thymectomy; 23 were investigated only after thymectomy.

2. Urinary pregnanediol was estimated as a measure of progesterone elaboration and metabolism in the organism.

3. Urinary pregnanediol in myasthenia gravis is at the lowest limit of normal or well below it.

4. After thymectomy pregnanediol excretion increases rapidly. Within three weeks of operation it may be four times as great as before thymectomy, and may be above the normal limits of excretion. More than two years after thymectomy pregnanediol excretion may be eight to 10 times the normal.

5. After the injection of progesterone in myasthenic patients less than half the normal amount is recovered as pregnanediol in the urine. Within a few days of thymectomy the recovery of injected progesterone is within normal limits.

6. Injection of corticotrophin in myasthenic patients eliminates pregnanediol in very large quantities. After thymectomy injection of corticotrophin causes the excretion of the same quantities as are found in normal subjects.

7. The place of the thymus in myasthenia gravis in relation to progesterone metabolism is discussed.

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# A FIVE-YEAR ASSESSMENT OF PATIENTS IN A CONTROLLED TRIAL OF STREPTOMYCIN WITH DIFFERENT DOSES OF PARA-AMINOSALICYLIC ACID IN PULMONARY TUBERCULOSIS[1]

*Report to the Tuberculosis Chemotherapy Trials Committee of the Medical Research Council*

BY WALLACE FOX AND IAN SUTHERLAND

(From the Tuberculosis and Statistical Research Units of the Medical Research Council)

IN 1949 a joint sub-committee of the Streptomycin in Tuberculosis Trials Committee of the Medical Research Council and the Research Committee of the British Tuberculosis Association planned a controlled clinical trial of streptomycin with different doses of *p*-aminosalicylic acid (PAS) in the treatment of pulmonary tuberculosis. Patients with acute extensive disease were allocated at random to three series; all the patients received streptomycin, 1 g. daily for three months, in combination with PAS (sodium) in dosages of 20 g., 10 g., or 5 g. daily. Detailed results after six months' observation have already been published (Medical Research Council, 1952). In all the clinical and radiographic assessments the progress of the three groups was similar. There were, however, important differences between the groups in the incidence of streptomycin-resistant strains of bacteria, the proportion being least for the patients receiving PAS (sodium) 20 g. daily, and greatest for those receiving PAS (sodium) 5 g. daily. The present report gives the results of a follow-up of the three series of patients for a period of five years after admission to the trial. It represents a study parallel to the five-year assessments of the two earlier Medical Research Council controlled trials of streptomycin and PAS in pulmonary tuberculosis (Fox, Sutherland, and Daniels, 1954; Fox and Sutherland, 1956).

## I. *Plan and Conduct of the Trial*

*The type of case* included in the trial was defined as follows: acute, progressive, bilateral pulmonary tuberculosis, believed to be of recent origin, bacteriologically proved, and unsuitable for collapse therapy; age-group 15 to 30 years. All cases were reviewed by a central panel of clinicians before acceptance, to ensure that they conformed to this definition. Each patient was admitted to one of 10 co-operating centres, and allocated to one of the three treatment series by reference to a list based upon random sampling numbers, held confidentially in

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the Council's Tuberculosis Research Unit. Of 115 patients studied in the trial, 42 were allocated to the combination of streptomycin with PAS (sodium) 20 g. (SP 20 series), 39 to the combination with PAS (sodium) 10 g. (SP 10 series) and 34 to the combination with PAS (sodium) 5 g. (SP 5 series).

*Treatment and observation.* All the patients were admitted to the trial between November 1949 and December 1950. After a week of preliminary investigation and assessment, each patient entered the trial for a period of six months, and the treatment allocated was prescribed for the first three months. The streptomycin was given in one intramuscular injection daily; the PAS was given by mouth in four equal doses daily. All the patients remained in bed for at least the six-month period, and during this time regular clinical, bacteriological, and radiographic observations were made. From three months onwards the clinician was free to prescribe any treatment he wished for any patient.

*Two-year and five-year assessment.* After the six-month assessment the subsequent progress of the patients was studied at the end of two years after entry to the trial, and again at the end of five years. Assessments of clinical condition at the end of two and five years were obtained, together with details of the treatment which each patient had received during the five-year period. Whenever possible a complete series of radiographs was assembled for independent assessment. Bacteriological analyses were impracticable, since in many of the surviving patients, both at two and at five years, active disease was no longer present, and examinations for tubercle bacilli had been performed very infrequently. All the patients were traced.

## II. *Comparability of the Three Treatment Series*

*Interpretation of long-term comparisons.* It was shown in the earlier report (Medical Research Council, 1952) that the distribution of patients according to clinical condition on admission was broadly similar in the three series, but there were rather more patients severely ill in the SP 10 series than in the other two. Thus, during the first three months, it was legitimate to relate the differences in progress observed to the differences in chemotherapy. After three months each clinician was free to institute whatever treatment he felt would then most benefit the patient, although it was strongly recommended that in the second three months any further chemotherapy combining the two drugs should not be different in dosage from that given in the first three months. In interpreting long-term results it is thus essential to know what additional chemotherapy and collapse therapy were given to each patient during the five-year period, and whether there were any notable differences between the series in these respects.

*Additional chemotherapy during the five-year period.* The details are set out in Table I. Of the 42 SP 20 patients 74 per cent. received additional chemotherapy during the five-year period, compared with 74 per cent. of the 39 SP 10 and 62 per cent. of the 34 SP 5 patients, the average duration of chemotherapy for those who received it being 8·0, 7·8, and 7·7 months respectively. Most of the

chemotherapy consisted of combinations of two or more drugs; in the first two years the combination used was almost invariably streptomycin with PAS, but thereafter streptomycin with isoniazid and PAS with isoniazid were also given. Single-drug therapy, when it was given, usually consisted of a course of PAS alone. The proportion of patients who received chemotherapy was less in the SP 5 series than in the other two series, for each of the three sub-periods identified in Table I.

TABLE I

*Additional Chemotherapy during the Five-Year Period*

| | | *Period 3 months–5 years* | | | | | | *Patients receiving any form of chemotherapy at some time during the period* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Patients receiving any form of chemotherapy* | | | *Patients receiving combined chemotherapy* | | | *3 months–1 year* | | *1–2 years* | | *2–5 years* | |
| *Treatment allocated for the first 3 months* | *Total patients* | *Number* | *%* | *Average total duration (months)* | *Number* | *%* | *Average total duration (months)* | *Number* | *% of total patients* | *Number* | *% of survivors at 1 year* | *Number* | *% of survivors at 2 years* |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 42 | 31 | *74* | 8·0 | 28 | *67* | 7·4 | 13 | *31* | 13 | *32* | 21 | *57* |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 39 | 29 | *74* | 7·8 | 27 | *69* | 6·0 | 15 | *38* | 13 | *36* | 20 | *61* |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 34 | 21 | *62* | 7·7 | 19 | *56* | 6·9 | 9 | *26* | 5 | *17* | 14 | *48* |

TABLE II

*Patients with Collapse Therapy or Resection during the Five-Year Period*

| | *Period 3 months–5 years* | | | *Patients with collapse therapy or resection at some time during the period* | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Patients with collapse therapy or resection* | | | *3 months–1 year* | | *1–2 years* | | *2–5 years* | |
| *Treatment allocated for the first 3 months* | *Total patients* | *Number* | *%* | *Number* | *% of total patients* | *Number* | *% of survivors at 1 year* | *Number* | *% of survivors at 2 years* |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 42 | 26 | *62* | 20 | *48* | 22 | *54* | 23 | *62* |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 39 | 28 | *72* | 24 | *62* | 24 | *67* | 21 | *64* |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 34 | 21 | *62* | 15 | *44* | 15 | *50* | 20 | *69* |

*Collapse therapy and resection during the five-year period.* To simplify the presentation of the complex pattern of collapse therapy and resection, several conventions have been adopted. A reversible form of collapse therapy has been regarded as established, and included in the Tables, only if it was maintained for a period of at least three months. It is certain that in some patients a phrenic nerve crush or re-crush has not been reported, and so these measures have been excluded. Since a resection and a thoracoplasty are often associated,

it was decided that when both measures were applied to the same lung the treatment would be recorded as a resection, whichever operation was performed first, and irrespective of the interval between them. The numbers of patients who had collapse therapy or resection are given in Table II. Of the SP 20 patients, 62 per cent. had some form of intervention in the five years, compared with 72 per cent. of the SP 10 and 62 per cent. of the SP 5 patients. In the

TABLE III

*The Types of Collapse Measure and Resection during the Five-Year Period*

| *Treatment allocated for the first 3 months* | *Total patients with collapse measures or resection* | *Total procedures* | *Procedure* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Artificial pneumothorax* | | | | | *Resection* | |
| | | | *Pneumoperitoneum* | *Unilateral* | *Bilateral* | *Thoracoplasty* | *Plombage* | *Extrapleural pneumothorax* | *Whole lung* | *Lobe or segment* |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 26 | 43 | 22 | 5 | 2 | 9 | 1 | 0 | 2 | 2 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 28 | 43 | 19 | 7 | 2 | 7 | 4* | 0 | 0 | 4 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 21 | 30 | 9 | 6 | 0 | 9 | 3 | 1 | 0 | 2 |

* One of these became infected and was converted to a thoracoplasty after four months.

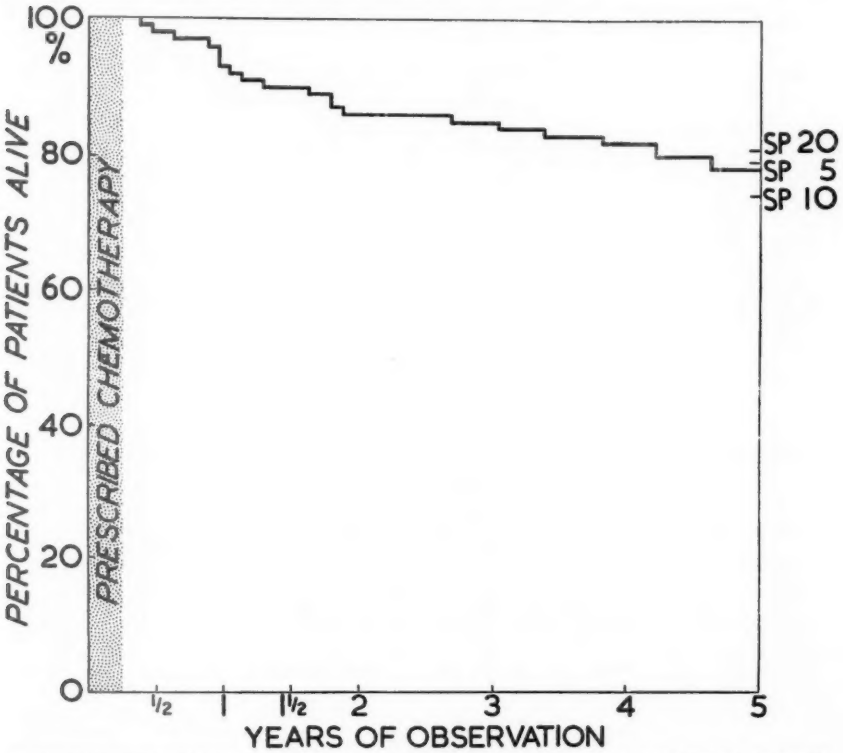
TABLE IV

*Mortality in the Three Treatment Series during the Five-Year Period*

| *Treatment allocated for the first 3 months* | *Total patients* | *Deaths in the first* | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *6 months* | | *1 year* | | *18 months* | | *2 years* | | *2½ years* | | *3 years* | | *3½ years* | | *4 years* | | *4½ years* | | *5 years* | |
| | | *Number* | % | *Number* | % | *Number* | % | *Number* | % | *Number* | % | *Number* | % | *Number* | % | *Number* | % | *Number* | % | *Number* | % |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 42 | 0 | *0* | 1 | *2* | 2 | *5* | 5 | *12* | 5 | *12* | 5 | *12* | 7 | *17* | 8 | *19* | 8 | *19* | 8 | *19* |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 39 | 0 | *0* | 3 | *8* | 5 | *13* | 6 | *15* | 6 | *15* | 7 | *18* | 8 | *21* | 8 | *21* | 9 | *23* | 10 | *26* |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 34 | 2 | *6* | 4 | *12* | 4 | *12* | 5 | *15* | 5 | *15* | 5 | *15* | 5 | *15* | 5 | *15* | 6 | *18* | 7 | *21* |

first two years a higher proportion of the patients in the SP 10 series had collapse therapy or resection than in the other two series; between two and five years the proportions in the three series were similar. Table III classifies the types of collapse measure and resection. There were 43 procedures in 26 SP 20 patients, 43 in 28 SP 10 patients, and 30 in 21 SP 5 patients. There were 22 pneumoperitoneums in the SP 20, 19 in the SP 10, and nine in the SP 5 series. Artificial pneumothorax was also a common procedure, being used in seven, nine, and

six patients respectively; a bilateral pneumothorax was used in only four of these patients. Thoracoplasty or plombage was used in 10 SP 20, 11 SP 10, and 12 SP 5 patients. There were four resections in the SP 20, four in the SP 10, and two in the SP 5 series. Apart from the smaller number of pneumoperitoneums in the SP 5 series, collapse therapy, both reversible and permanent, was used with similar frequency in the three series.




Percentage survival in the three treatment series for a five-year period (42 SP 20, 39 SP 10, and 34 SP 5 patients).

*Chemotherapy in the fifth year and reversible collapse therapy at five years.* Active therapy was still required towards the end of the five-year period in a substantial number of patients. Ten of the SP 20, nine of the SP 10, and three of the SP 5 survivors received chemotherapy in the fifth year, and at the end of five years three of the survivors in each series still had an artificial pneumothorax or pneumoperitoneum.

### III. *Results during the Five-Year Period*

*The mortality in the five-year period* is analysed in Table IV and the Figure. All deaths were due to pulmonary tuberculosis. By the end of five years 19 per cent. of the SP 20, 26 per cent. of the SP 10, and 21 per cent. of the SP 5 patients

had died. The differences between the mortalities in the three series throughout the period are unimportant. In the three series combined, the majority of the deaths, 16 of 25, occurred in the first two years.

TABLE V

*Mortality and Disease Status of Patients, and Working Capacity of Survivors, in the Three Treatment Series at Two Years*

| Treatment allocated for the first 3 months | Total patients | | Status of patients: Quiescent disease | | Active disease | | Dead | | Total survivors at 2 years | | Working capacity of survivors: Full activity | | Modified activity | | Nil | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 42 | 100 | 15 | 36 | 22 | 52 | 5 | 12 | 37 | 100 | 5 | 14 | 9 | 24 | 23 | 62 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 38* | 100 | 13 | 34 | 19 | 50 | 6 | 16 | 32 | 100 | 5 | 16 | 3 | 9 | 24 | 75 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 34 | 100 | 15 | 44 | 14 | 41 | 5 | 15 | 29 | 100 | 8 | 28 | 4 | 14 | 17 | 59 |

* For one more patient no assessment was possible at two years.

TABLE VI

*Changes in Radiographic Appearances in the Three Treatment Series in the First Two Years*

| Treatment allocated for the first 3 months | Total patients assessed | | Improvement: Exceptional | | Considerable | | Moderate | | Slight | | No change | | Slight deterioration | | Death | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 39* | 100 | 1 | 3 | 12 | 31 | 14 | 36 | 5 | 13 | 1 | 3 | 1 | 3 | 5 | 13 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 36* | 100 | 2 | 6 | 10 | 28 | 11 | 31 | 5 | 14 | 0 | 0 | 2 | 6 | 6 | 17 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 30* | 100 | 0 | 0 | 8 | 27 | 11 | 37 | 4 | 13 | 1 | 3 | 1 | 3 | 5 | 17 |

* For three SP 20, three SP 10, and four SP 5 patients one or the other radiograph was not available.

*Clinical assessment at two years.* The disease in the survivors at two years was classified by the clinician in charge as 'quiescent' or 'active'; the working capacity was reported as 'full activity', 'modified activity', or 'nil' (for definitions see the Appendix). The first part of Table V shows the mortality and disease status of patients in the three series at two years. Of the SP 20 patients 36 per cent. had attained quiescence, compared with 34 per cent. of SP 10 and 44 per cent. of the SP 5 patients. The majority of the survivors (second part of Table V) were still classified as having no working capacity, namely 62 per cent. of the SP 20, 75 per cent. of the SP 10, and 59 per cent. of the SP 5 survivors. In both respects the SP 10 series had not fared quite as well as the other two series.

*Radiographic changes in the first two years* were assessed by a panel consisting of two radiologists (Drs. L. G. Blair and G. Simon) and a chest physician (Dr. A. F. Foster-Carter). In making their assessments the members were unaware to which treatment series each patient had been allocated. Four degrees of improvement were allowed: slight, moderate, considerable, and exceptional; and three of deterioration: slight, moderate, and considerable.

TABLE VII

*Mortality and Disease Status of Patients, and Working Capacity of Survivors, in the Three Treatment Series at Five Years*

| Treatment allocated for the first 3 months | Total patients assessed | Status of patients: Arrested disease | | Quiescent disease | | Active disease | | Dead | | Total survivors at 5 years | | Working capacity of survivors: Full activity | | Modified activity | | Nil | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 41* | 12 | 29 | 15 | 37 | 6 | 15 | 8 | 20 | 34 | 100 | 20 | 59 | 3 | 9 | 11 | 32 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 38* | 8 | 21 | 9 | 24 | 11 | 29 | 10 | 26 | 29 | 100 | 13 | 45 | 6 | 21 | 10 | 34 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 34 | 8 | 24 | 13 | 38 | 6 | 18 | 7 | 21 | 27 | 100 | 20 | 74 | 2 | 7 | 5 | 19 |

* For one more patient no assessment of disease status was possible at five years.

TABLE VIII

*Changes in Radiographic Appearances in the Three Treatment Series in the Five-Year Period*

| Treatment allocated for the first 3 months | Total patients assessed | Improvement: Exceptional | | Considerable | | Moderate | | Slight | | No change | | Slight deterioration | | Death | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % | Number | % |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 41* | 4 | 10 | 21 | 51 | 7 | 17 | 1 | 2 | 0 | 0 | 0 | 0 | 8 | 20 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 38* | 3 | 8 | 18 | 47 | 5 | 13 | 0 | 0 | 1 | 3 | 1 | 3 | 10 | 26 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 34 | 2 | 6 | 20 | 59 | 2 | 6 | 3 | 9 | 0 | 0 | 0 | 0 | 7 | 21 |

*For one more patient one or the other radiograph was not available.

In evaluating changes in the first two years, the radiographs taken on entry to the trial and at two years were used; intermediate films were studied if they were available and were requested. The panel assessments were undertaken and collated in the manner already described (Fox, Sutherland, and Daniels, 1954). No comparisons were possible for the first two years for three SP 20, three SP 10, and four SP 5 patients, for whom relevant radiographs had been destroyed, mislaid, or not taken. The available results are presented in Table VI, and show a close similarity between the series. Of 39 SP 20 patients 33 per cent. showed considerable or exceptional improvement, compared with 33 per

cent. of 36 SP 10 and 27 per cent. of 30 SP 5 patients. Only four of the survivors showed radiographic deterioration in the first two years.

*Changes in cavitation in the first two years* were assessed from the single postero-anterior radiographs taken on entry to the trial and at two years. Cavitation had disappeared in 17 (59 per cent.) of 29 SP 20 patients with initial cavitation, in 15 (58 per cent.) of 26 SP 10 patients, and in 12 (57 per cent.) of 21 SP 5 patients. At the end of two years cavitation was visible on a standard radiograph in 12 (35 per cent.) of the 34 SP 20, 11 (37 per cent.) of the 30 SP 10, and nine (36 per cent.) of the 25 SP 5 patients. The three series had fared similarly, and the results have not been tabulated.

*Clinical assessment at five years.* The disease in patients who survived five years was classified as 'arrested', 'quiescent', or 'active', and their working capacity as 'full activity', 'modified activity', or 'nil' (for definitions see the Appendix). The assessments are given in Table VII. The disease was arrested or quiescent in 66 per cent. of SP 20, in 45 per cent. of SP 10, and in 62 per cent. of SP 5 patients. The SP 10 series had not fared so well as the other two series. The majority of survivors had returned to employment, but 32 per cent. of SP 20, 34 per cent. of SP 10, and 19 per cent. of the SP 5 survivors had no working capacity.

*The radiographic changes in the five-year period* were evaluated by the panel, using single radiographs taken on entry to the trial, at two years, and at five years, with intermediate films if these were requested. The radiographs were read by the panel members at sessions subsequent to those held for the two-year study. Relevant radiographs were not available for one SP 20 and one SP 10 patient; the results for the remaining patients are presented in Table VIII. Of the SP 20 patients 61 per cent. showed considerable or exceptional improvement, compared with 55 per cent. of the SP 10 and 65 per cent. of the SP 5 patients. Nearly all the survivors showed at least moderate improvement. Only one survivor, an SP 10 patient, showed radiographic deterioration over the five-year period. The findings for the three series were similar.

*Changes in cavitation in the five-year period* in the survivors are shown in Table IX. Changes were assessed from single postero-anterior radiographs taken on entry to the trial and at five years, and from the tomograms which were also available for some patients. Cavitation had disappeared in 82 per cent. of 28 SP 20 survivors who initially had cavitation, in 75 per cent. of 24 SP 10, and in 73 per cent. of 22 SP 5 survivors. In the three series combined, no cavitation was apparent initially in 14 patients, and they still had none at the end of five years. Even at the end of five years 17 (19 per cent.) of the total of 88 survivors had cavitation.

*Nature of radiographic improvements in the five-year period.* The standard radiographs taken on entry to the trial and at the end of five years, for all the patients in whom radiographic improvement occurred, were submitted to a single independent observer (Dr. G. Simon) for appraisal of the nature of the improvements; only major changes were recorded. Improvement was classified under the following headings: resolution, fibrosis, calcification, lobar or

segmental atelectasis, reduction of cavitation, and disappearance of cavitation (see the Appendix). Resolution was reported in every patient (Table X). Disappearance or reduction of cavitation was a major improvement in 26 of 28 SP 20 patients with initial cavitation, in 22 of 24 SP 10, and in 18 of the 22 SP 5 patients. Calcification occurred in 11 SP 20, 15 SP 10, and nine SP 5 patients.

TABLE IX

*Changes in Cavitation on Standard Radiographs in the Three Treatment Series in the Five-Year Period*

| *Treatment allocated for the first 3 months* | *Total survivors at 5 years* | *Survivors without initial cavitation* | | *Survivors with initial cavitation* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Total* | *Disappearance of cavitation* | | *Cavities smaller or fewer* | | *No change* | | *Cavities larger or more numerous* | |
| | | *Total* | *Appearance of cavitation* | *Number* | *Number* | *%* | *Number* | *%* | *Number* | *%* | *Number* | *%* |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 33* | 5 | 0 | 28 | 23 | *82* | 3 | *11* | 2 | *7* | 0 | *0* |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 28* | 4 | 0 | 24 | 18 | *75* | 4 | *17* | 0 | *0* | 2 | *8* |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 27 | 5 | 0 | 22 | 16 | *73* | 3 | *14* | 3 | *14* | 0 | *0* |

* For one more patient one or other radiograph was not available.

TABLE X

*Nature of Major Changes in Radiographic Appearances for Patients who showed Radiographic Improvement in the Five-Year Period*

| *Treatment allocated for the first 3 months* | *Total patients with radiographic improvement* | *Major radiographic changes* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Resolution* | *Disappearance of cavitation* | | | *Reduction in cavitation* | *Fibrosis* | *Calcification* | *Lobar atelectasis* |
| | | | *Without resection* | *Some cavities resected* | *All cavities resected* | | | | |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 33* | 33 | 19 | 2 | 2 | 3 | 11 | 11 | 2 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 26* | 26 | 14 | 2 | 2 | 4 | 4 | 15 | 1 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 27 | 27 | 15 | 1 | 0 | 2 | 4 | 9 | 3 |

* For one more patient no assessment of major changes was possible at five years.

Fibrosis was less frequent, except in the SP 20 series, where it was observed as a major change in 11 patients. There were, in all, six instances of atelectasis. The major radiographic improvements thus consisted of resolution and

disappearance of cavitation, and the nature of the improvements was similar in the three series.

The mortality and course of the disease in the three treatment series have now been described. In the following section a study is made of the extent to which the outcome in each series depended on the condition of the patients on admission to the trial, and on their response to treatment during the first three months.

### IV. *Prognostic Factors in Acute Bilateral Pulmonary Tuberculosis in Young Adults*

A study has been made of the extent to which the initial clinical condition and the immediate response to treatment affected the prognosis. The mortality during the five-year period and the disease status of the survivors have in each series been related to the condition of the patients on admission to the trial, as judged by extent of cavitation, temperature, erythrocyte sedimentation

TABLE XI

*Mortality and Disease Status at Five Years, according to the Extent of Initial Cavitation**

| *Treatment allocated for the first 3 months* | *Extent of initial cavitation* | *Total patients* | *Death within 5 years* | *Disease status of survivors at 5 years* | | |
|---|---|---|---|---|---|---|
| | | | | *Active* | *Quiescent* | *Arrested* |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 3-plus | 8 | 5† | 2 | 0 | 1 |
| | 2-plus | 17 | 3 | 2 | 6 | 6 |
| | 1-plus | 11‡ | 0 | 2 | 7* | 2 |
| | Nil | 5 | 0 | 0 | 2 | 3 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 3-plus | 7‡ | 4 | 3 | 0 | 0 |
| | 2-plus | 17 | 3 | 5 | 4 | 5 |
| | 1-plus | 9 | 2 | 2 | 4 | 1 |
| | Nil | 5 | 1 | 1 | 1 | 2 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 3-plus | 7 | 3 | 2 | 1 | 1 |
| | 2-plus | 12 | 4 | 3 | 4 | 1 |
| | 1-plus | 10 | 0 | 1 | 6 | 3 |
| | Nil | 5 | 0 | 0 | 2 | 3 |
| All treatment series | 3-plus | 22 | 12 | 7 | 1 | 2 |
| | 2-plus | 46 | 10 | 10 | 14 | 12 |
| | 1-plus | 30 | 2 | 5 | 17 | 6 |
| | Nil | 15 | 1 | 1 | 5 | 8 |

* Recent reassessment. For details see text.

† Including one patient for whom the radiograph on admission was not available, and the earlier assessment of extent of initial cavitation was used.

‡ For one more patient no assessment of disease status was possible at five years.

rate (Westergren), and the number of lung zones involved (on a standard radiograph). The mortality and disease status have also been related to sex and to the response to treatment during the first three months, as indicated by changes in the radiographs, erythrocyte sedimentation rate, temperature, and sputum positivity, and by the emergence of drug-resistant bacteria.

*Cavitation on admission.* A reassessment of the extent of cavitation on admission to the trial has recently been made by Dr. L. G. Blair, who assessed the extent of cavitation for the five-year follow-up of the two earlier chemotherapy trials (Fox, Sutherland, and Daniels, 1954; Fox and Sutherland, 1956). The reassessment incorporates the modification of technique used in the second of

these reports. The assessments have been used to study mortality and disease status in relation to initial cavitation (Table XI). Combining the figures for all three treatments, 55 per cent. of 22 patients with 3-plus cavitation on admission were dead within five years, compared with 22 per cent. of 46 with 2-plus cavitation, 7 per cent. of 30 with 1-plus cavitation, and 7 per cent. of 15 with no cavitation. The pattern in each treatment series is similar. Considering the survivors at the end of five years, those who initially had extensive cavitation more frequently had active disease at the end of the period than those with little or no initial cavitation.

TABLE XII

*Mortality and Disease Status at Five Years, according to Temperature on Admission*

| *Treatment allocated for the first 3 months* | *Average evening temperature during week of preliminary investigation* | *Total patients* | *Death within 5 years* | *Disease status of survivors at 5 years* | | |
|---|---|---|---|---|---|---|
| | | | | *Active* | *Quiescent* | *Arrested* |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 100° F or more | 7 | 2 | 0 | 2 | 3 |
| | 99°–99·9° F | 16 | 2 | 5 | 5 | 4 |
| | Under 99° F | 14 | 4 | 1 | 5 | 4 |
| | No fever | 4* | 0 | 0 | 3 | 1 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 100° F or more | 9* | 5 | 1 | 1 | 2 |
| | 99°–99·9° F | 14 | 2 | 5 | 4 | 3 |
| | Under 99° F | 9 | 2 | 3 | 2 | 2 |
| | No fever | 6 | 1 | 2 | 2 | 1 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 100° F or more | 4 | 3 | 1 | 0 | 0 |
| | 99°–99·9° F | 15 | 2 | 2 | 6 | 5 |
| | Under 99° F | 7 | 1 | 1 | 3 | 2 |
| | No fever | 8 | 1 | 2 | 4 | 1 |
| All treatment series | 100° F or more | 20 | 10 | 2 | 3 | 5 |
| | 99°–99·9° F | 45 | 6 | 12 | 15 | 12 |
| | Under 99° F | 30 | 7 | 5 | 10 | 8 |
| | No fever | 18 | 2 | 4 | 9 | 3 |

* For one more patient no assessment of disease status was possible at five years.

*Temperature on admission.* Table XII relates the mortality and disease status in the three series to the average evening temperature during the week of preliminary observation. A similar pattern appears as for cavitation, the most febrile patients having the worst prognosis. Thus, for the three series combined, 50 per cent. of the 20 patients with an average evening temperature of 100° F or more died within five years, compared with 16 per cent. of the 93 patients who were in the lower categories of pyrexia or who were apyrexial.

*Other criteria on admission.* A similar association was observed between the erythrocyte sedimentation rate and the mortality in each of the three treatment series. Of 53 patients with a sedimentation rate of 51 mm. in an hour on admission, or more, 16 (30 per cent.) had died within five years, compared with nine (18 per cent.) of 50 patients with a sedimentation rate of 21 to 50 mm. and none of 10 patients with a sedimentation rate of 20 mm. or less. The patterns were similar in each of the three treatment series; the results have not been tabulated. No association was apparent between the number of lung zones involved and the mortality within five years. The sex differences in mortality and disease status at the end of five years were unimportant.

*Mortality and disease status related to early radiographic response.* Table XIII presents the mortality during the five-year period, and the disease status of the survivors, in relation to radiographic changes during the first three months, as assessed by the original radiological panel (Medical Research Council, 1952). Of 46 patients, in the three series combined, who had failed to improve radiographically during this period, 33 per cent. died within the five years, compared with 15 per cent. of 67 who had shown radiographic improvement; this difference is significant at the 5 per cent. level. The findings for the three series separately were similar. Thus failure to show early radiographic improvement was of prognostic importance in each of the three series. Similar findings emerged from an analysis of mortality in relation to the radiographic changes in the first six months.

TABLE XIII

*Mortality and Disease Status at Five Years, according to Changes in Radiographic Appearances in the First Three Months**

| *Treatment allocated for the first 3 months* | *Changes in radiographic appearances in the first 3 months** | *Total patients* | *Death within 5 years* | *Disease status of survivors at 5 years* | | |
|---|---|---|---|---|---|---|
| | | | | *Active* | *Quiescent* | *Arrested* |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | Deterioration or no change | 18 | 4 | 3 | 7 | 4 |
| | 1-plus improvement | 21† | 4 | 2 | 7 | 8 |
| | 2-plus or 3-plus improvement | 2 | 0 | 1 | 1 | 0 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | Deterioration or no change | 18 | 8 | 4 | 3 | 3 |
| | 1-plus improvement | 18† | 2 | 6 | 6 | 4 |
| | 2-plus or 3-plus improvement | 2 | 0 | 1 | 0 | 1 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | Deterioration or no change | 10 | 3 | 3 | 2 | 2 |
| | 1-plus improvement | 22 | 4 | 2 | 11 | 5 |
| | 2-plus or 3-plus improvement | 2 | 0 | 1 | 0 | 1 |
| All treatment series | Deterioration or no change | 46 | 15 | 10 | 12 | 9 |
| | 1-plus improvement | 61 | 10 | 10 | 24 | 17 |
| | 2-plus or 3-plus improvement | 6 | 0 | 3 | 1 | 2 |

* As assessed in the earlier report (Medical Research Council, 1952).
† For one more patient no assessment of disease status was possible at five years.

*Mortality and disease status related to early clinical response.* Early changes in the erythrocyte sedimentation rate were also of some prognostic importance. Of the 11 patients, in all three series combined, in whom the sedimentation rate rose or remained at the same level in the first three months, six (55 per cent.) had died within five years, compared with 19 deaths (19 per cent.) among the 102 patients in whom the sedimentation rate fell. Similarly, of the 15 patients who either became febrile or in whom the temperature did not fall in the first three months, eight (53 per cent.) died within five years, compared with 17 deaths (17 per cent.) among the 98 patients in whom the temperature fell, or who were apyrexial both on admission and at the end of three months. These results have not been tabulated.

*Mortality and disease status related to early bacteriological response.* In Table XIV the mortality and disease status at five years are related to the bacterial content of the sputum at three months. In this Table a single test has been recorded for each patient, namely, that nearest to the date of completion of the prescribed chemotherapy, provided that this was within a week of three months.

There is some association between the mortality in the five-year period and the bacterial content of the sputum at the end of three months. Of the 23 patients, in all three series combined, who had had a positive result on direct examination at three months, 35 per cent. died within five years, compared with 26 per cent. of 27 patients with results positive only on culture and 15 per cent. of 46 patients with results negative both on direct examination and on culture.

TABLE XIV

*Mortality and Disease Status at Five Years, according to Bacterial Content of the Sputum at Three Months*

| *Treatment allocated for the first 3 months* | *Results of single bacteriological examinations at 3 months* | | *Total patients with specimens tested* | *Death within 5 years* | *Disease status of survivors at 5 years* | | |
|---|---|---|---|---|---|---|---|
| | *Direct examination* | *Culture* | | | *Active* | *Quiescent* | *Arrested* |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | Positive | Positive or negative | 10* | 3 | 1 | 3 | 3 |
| | Negative | Positive | 6 | 2 | 0 | 2 | 2 |
| | Negative | Negative | 20 | 3 | 4 | 7 | 6 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | Positive | Positive or negative | 9 | 5 | 2 | 1 | 1 |
| | Negative | Positive | 13 | 2 | 5 | 3 | 3 |
| | Negative | Negative | 12* | 2 | 3 | 5 | 2 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | Positive | Positive or negative | 4 | 0 | 2 | 0 | 2 |
| | Negative | Positive | 8 | 3 | 1 | 2 | 2 |
| | Negative | Negative | 14 | 2 | 2 | 7 | 3 |
| All treatment series | Positive | Positive or negative | 23 | 8 | 5 | 4 | 6 |
| | Negative | Positive | 27 | 7 | 6 | 7 | 7 |
| | Negative | Negative | 46 | 7 | 9 | 19 | 11 |

* For one more patient no assessment of disease status was possible at five years.

*Mortality and disease status related to the emergence of streptomycin-resistant bacteria.* No information as to streptomycin resistance is available for three patients (one in each of the three series), and for two more patients no assessment of disease status was possible at five years. Of the remaining 110 patients, 36 (33 per cent.) yielded resistant bacilli at some time during the six months.[2] Resistant bacilli were found in six (15 per cent.) of the 40 SP 20, 13 (35 per cent.) of the 37 SP 10, and 17 (52 per cent.) of the 33 SP 5 patients. In Table XV the mortality and disease status at five years are related to the highest streptomycin-resistance ratio obtained during the first six months. Of 14 patients with a resistance ratio of 100 or more in the three series combined, 43 per cent. had died, compared with 36 per cent. of 22 patients with less resistant strains and 15 per cent. of 74 patients with sensitive strains. The association was similar in each of the three series. It cannot, however, be concluded from these figures that the emergence of resistance necessarily had a direct influence on the subsequent

[2] Taking a resistance ratio of 8×H37Rv as the lower limit of resistance. One SP 5 patient has been added to the resistant group since the publication of the earlier report (Medical Research Council, 1952).

course of the disease, for, as was shown in the earlier report (Medical Research Council, 1952), the patients who developed streptomycin resistance were, as a group, more acutely ill on admission to the trial.

TABLE XV

*Mortality and Disease Status at Five Years, according to Bacterial Resistance to Streptomycin during the First Six Months*

| *Treatment allocated for the first 3 months* | *Highest streptomycin resistance ratio during the first 6 months* | *Total patients with information available* | *Death within 5 years* | *Disease status of survivors at 5 years* | | |
|---|---|---|---|---|---|---|
| | | | | *Active* | *Quiescent* | *Arrested* |
| Streptomycin plus PAS (sodium) 20 g. (SP 20) | 100 or more | 1 | 0 | 1 | 0 | 0 |
| | 8–99 | 5* | 3 | 0 | 1 | 1 |
| | Under 8 | 34 | 5 | 5 | 14 | 10 |
| Streptomycin plus PAS (sodium) 10 g. (SP 10) | 100 or more | 6 | 2 | 3 | 0 | 1 |
| | 8–99 | 7* | 3 | 1 | 2 | 1 |
| | Under 8 | 24 | 5 | 7 | 6 | 6 |
| Streptomycin plus PAS (sodium) 5 g. (SP 5) | 100 or more | 7 | 4 | 2 | 0 | 1 |
| | 8–99 | 10† | 2 | 1 | 6 | 1 |
| | Under 8 | 16 | 1 | 3 | 6 | 6 |
| All treatment series | 100 or more | 14 | 6 | 6 | 0 | 2 |
| | 8–99 | 22 | 8 | 2 | 9 | 3 |
| | Under 8 | 74 | 11 | 15 | 26 | 22 |

* For one more patient no assessment of disease status was possible at five years.
† One patient has been transferred to this group from the 'under 8' group since the publication of the earlier report (Medical Research Council, 1952).

TABLE XVI

*Mortality and Disease Status at Five Years, according to the Extent of Initial Cavitation* and Bacterial Resistance to Streptomycin during the First Six Months*

| *Extent of initial cavitation* | *Highest streptomycin resistance ratio during the first 6 months* | *Total patients with information available* | *Death within 5 years* | *Disease status of survivors at 5 years* | | |
|---|---|---|---|---|---|---|
| | | | | *Active* | *Quiescent* | *Arrested* |
| 3-plus | 100 or more | 7 | 3 | 4 | 0 | 0 |
| | 8–99 | 6‡ | 5† | 0 | 1 | 0 |
| | Under 8 | 9 | 4 | 3 | 0 | 2 |
| 2-plus | 100 or more | 5 | 2 | 2 | 0 | 1 |
| | 8–99 | 9 | 3 | 1 | 3 | 2 |
| | Under 8 | 31 | 5 | 7 | 10 | 9 |
| 1-plus | 100 or more | 1 | 0 | 0 | 0 | 1 |
| | 8–99 | 5‡ | 0 | 1 | 4 | 0 |
| | Under 8 | 22 | 2 | 4 | 12† | 4 |
| Nil | 100 or more | 1 | 1 | 0 | 0 | 0 |
| | 8–99 | 2 | 0 | 0 | 1 | 1 |
| | Under 8 | 12 | 0 | 1 | 4 | 7 |
| All degrees of cavitation | 100 or more | 14 | 6 | 6 | 0 | 2 |
| | 8–99 | 22 | 8 | 2 | 9 | 3 |
| | Under 8 | 74 | 11 | 15 | 26 | 22 |

* Recent reassessment. For details see text.
† Including one patient for whom the radiograph on admission was not available, and the earlier assessment of extent of initial cavitation was used.
‡ For one more patient no assessment of disease status was possible at five years.

Since the emergence of streptomycin-resistant strains is known to be related to the extent of initial cavitation (Medical Research Council 1948, 1950; Howlett, O'Connor, Sadusk, Swift, and Beardsley, 1949; Tucker, 1949), and since it has been shown above (Table XI) that the mortality and disease status at

five years are also closely related to the extent of initial cavitation, an attempt has been made to assess the relative importance of initial cavitation and bacterial resistance in the prognosis. Table XVI shows the mortality and disease status at five years according to the highest streptomycin-resistance ratio obtained during the first six months, for each degree of initial cavitation separately. Considering the patients with 3-plus cavitation initially, eight (62 per cent.) of the 13 with a resistance ratio of 8 or more died within five years, compared with four (44 per cent.) of the nine with sensitive organisms. Among those with 2-plus cavitation initially there were five deaths (36 per cent.) among the 14 patients who developed resistance, and five (16 per cent.) among the 31 who retained sensitive organisms. Although the numbers are small, there is some evidence of association between the outcome at five years and the presence of resistance during the first six months, among patients with the same extent of initial cavitation. Nevertheless, the extent of initial cavitation appears to be of greater importance in the prognosis than the emergence of streptomycin-resistant organisms.

Only three strains resistant to PAS were isolated during the first six months (Medical Research Council, 1952), so that no similar analyses for PAS resistance are possible.

### *Discussion*

This report presents a five-year follow-up of all the 115 patients in the Medical Research Council's third controlled clinical trial of chemotherapy in the treatment of pulmonary tuberculosis. The combinations studied were daily streptomycin with three different dosages of *p*-aminosalicylic acid (PAS), these treatments being allocated for a period of three months by a random procedure. All the patients were young adults with acute extensive bilateral disease, a particularly grave form of tuberculosis. A report (Medical Research Council, 1952) showed that at the end of six months' treatment the three series had made very similar progress, judged clinically and radiographically, but that there was a much lower incidence of streptomycin resistance in the patients who were given the largest daily dosage of PAS (20 g. sodium salt)—the SP 20 series—than in those who were given either 10 g. (SP 10 series) or 5 g. daily (SP 5 series).

After the first three months the additional chemotherapy and collapse therapy during the five-year period were very similar in the three series. Fewer patients in the SP 5 series received further chemotherapy than in the other two series, and collapse therapy was given more frequently in the first two years to patients in the SP 10 series than in the other two series. These differences in subsequent treatment, however, were only slight, and it seems probable that they reflect differences in the initial clinical condition of the patients in the three series. There were initially rather more patients severely ill in the SP 10 series (Medical Research Council, 1952) and rather fewer severely ill in the SP 5 series. Although there was a wide divergence between the series in the proportion of patients who developed streptomycin-resistant strains during the first six months (15 per cent. of the SP 20, 35 per cent. of the SP 10, and 52 per cent. of the

SP 5 series), this does not appear to have led to any differences in the subsequent treatment.

The mortality during the five-year period showed little difference in the three series, being 19 per cent. in the SP 20 series, 26 per cent. in the SP 10, and 21 per cent. in the SP 5 series. The percentages of patients with quiescent or arrested disease were 66 per cent., 45 per cent., and 62 per cent. respectively. The SP 10 series had fared least well, but this is probably a consequence of the initial clinical differences. In particular it should be noted that the differences in the proportions of patients who developed streptomycin-resistant organisms in the first six months have not been reflected in the outcome over the five-year period. It should not, however, be concluded that the emergence of streptomycin resistance is an event of no importance to the management of a patient. If all the patients in the three series had received long subsequent courses of combined chemotherapy, including streptomycin, it would have been possible to judge whether the development of streptomycin resistance had impaired the effectiveness of the subsequent chemotherapy. After the three-month period of prescribed chemotherapy in the trial, however, the amounts of chemotherapy given by the clinicians in charge were comparatively limited. About two-thirds of the patients received further chemotherapy, for an average duration of just under eight months, usually in several short courses spread over the whole period of four years and nine months. Thus the conditions did not favour an assessment of the importance of streptomycin resistance.

In spite of the advances in the standard of treatment in recent years, acute bilateral disease in these young adults, whose treatment started in 1950, was serious and incapacitating. Combining the three series, at two years 65 per cent. of the 98 surviving patients were classified as having no working capacity, and even at five years the proportion was as high as 29 per cent. of the 90 survivors. Also, at five years, 26 per cent. of the survivors had active disease, and cavitation was visible on a standard radiograph in 19 per cent.; thus many were presumably still infectious. As a further indication of the persistently serious nature of the disease, 22 patients received some chemotherapy in the fifth year, and at the end of the period nine still had reversible collapse measures.

An analysis was made of some of the clinical features on admission to the trial, to see how these affected the prognosis. Extensive initial cavitation, a high pyrexia on admission, and a high erythrocyte sedimentation rate, were unfavourable prognostic signs in all three series. No association, however, was apparent between the number of lung zones involved and the mortality in the five-year period. The outcome was also related to the immediate response to treatment. Failure to improve radiographically in the first three months, and failure of the sedimentation rate or the temperature to respond, each carried a relatively bad prognosis. Patients with streptomycin-resistant organisms also had a relatively poor prognosis, but this appears to have been more closely related to the extent of initial cavitation than to the presence or degree of streptomycin resistance.

It is of value to compare the five-year progress of the 42 patients in the SP 20

series in this trial with that of the 53 patients in the SP series in the second Medical Research Council trial (Fox and Sutherland, 1956), since the treatments for the first three months were identical. Daniels and Hill (1952) showed that the distribution of severe and less severe illness among all patients on admission was alike in the two trials, and this is also true as regards patients allocated to the SP 20 and the SP series. The recent reassessment, by one assessor, of the extent of cavitation on admission has confirmed the similarity of the two series in this important feature. Moreover, radiographic progress was very similar in the two series during the first six months of observation (Daniels and Hill, 1952). At the end of five years 81 per cent. of the patients in the SP 20 series in the third trial had survived, 66 per cent. having arrested or quiescent disease, compared with a survival rate of 81 per cent. in the second trial, 70 per cent. having arrested or quiescent disease. The long-term outcome was thus alike in the two trials. When compared, however, with an earlier group of patients with similar disease, treated only with rest in bed in the first six months after diagnosis (Medical Research Council, 1948; Fox, Sutherland, and Daniels, 1954), the present group has fared remarkably well. The five-year mortality in the present group was 22 per cent., compared with 67 per cent. in the earlier group.

In conclusion, it must be appreciated that the present study represents a five-year follow-up of patients with a particularly acute, extensive, and grave type of disease, who started treatment more than seven years ago. There have been many changes in the treatment of pulmonary tuberculosis during the past few years, and, judged by present standards, this group of patients was inadequately treated. Their fate may therefore seem to be of historical interest only. The efficacy of present treatment, however, can only be judged fully by its long-term results. Current methods will need, in due course, to stand comparison with the results obtained in earlier series such as that reported here.

We regret that it is not possible to name individually all of the large number of clinicians whose willing co-operation has made this investigation possible. They provided many clinical data, and lent the radiographs for independent assessment; we wish to thank them for the completeness of the resulting information.

## APPENDIX

The definitions of disease activity were taken from the Revision of Section I of the Appendix to the Ministry of Health Memorandum 37/T (Revised), with the one exception that no patient who still had a reversible form of collapse therapy was considered to have 'arrested' disease. The relevant definitions are:

'"*Active cases.*" Those not quiescent. All cases discharging tubercle bacilli within the preceding three months should be considered as "active".

'"*Quiescent.*" Cases in which the general condition and exercise tolerance are good, having regard to the extent of the lesion; which show no evidence of toxaemia; in which no tubercle bacilli have been found on three consecutive monthly examinations by stained film; and in which changes revealed by other

clinical investigations and by serial skiagrams point to retrogression of the tuberculous lesion.

' "*Arrested.*" Cases in which the disease has been "quiescent" for a continuous period of at least TWO years.'

The following definitions of working capacity were used: '*Full activity*': patient in full-time employment, or undertaking normal housework. '*Modified activity*': patient in part-time employment, or undertaking limited housework. '*Nil*': patient's activity severely limited, or patient confined to bed.

In the assessment of major radiographic changes the following definitions were adopted: *Resolution*: the disappearance or diminution in size of one or more of the lesions. *Fibrosis*: (*a*) appearance of linear shadows, or (*b*) diminution in size of lesions, associated with sharpening of their outline or increase in their density; often associated with evidence of lung shrinkage, such as displacement of the trachea, vessels, or a fissure. *Reduction in cavitation*: cavities smaller or fewer, or both, on postero-anterior radiographs. *Disappearance of cavitation*: disappearance of all cavitation on postero-anterior radiographs.

*Summary*

All the 115 patients in the Medical Research Council's third controlled clinical trial of chemotherapy in the treatment of pulmonary tuberculosis have now been followed for five years or until death. The patients, who were young adults with acute, bilateral, and progressive pulmonary tuberculosis of recent origin, were treated in hospital for six months, and were allocated at random to a three-month course of chemotherapy consisting of streptomycin 1 g. daily, in combination with *p*-aminosalicylic acid (PAS), sodium salt, in dosages of 20 g. daily (42 SP 20 patients), or of 10 g. daily (39 SP 10 patients), or of 5 g. daily (34 SP 5 patients).

On entry to the trial there were rather more patients severely ill in the SP 10 series, and rather fewer in the SP 5 series, than in the SP 20 series. After the first three months there were slight differences in subsequent treatment, which probably reflect the differences in the initial clinical condition of the patients in the three series. About two-thirds of the patients had some form of collapse therapy or resection during the five years; about two-thirds received further chemotherapy, for an average duration of just under eight months, usually in several short courses.

By the end of five years 19 per cent. of the SP 20, 26 per cent. of the SP 10, and 21 per cent. of the SP 5 patients, had died; 66 per cent. of the SP 20, 45 per cent. of the SP 10, and 62 per cent. of the SP 5 patients, had quiescent or arrested disease. The less satisfactory results in the SP 10 series are probably a consequence of the initial clinical differences.

By the end of the first six months 15 per cent. of the SP 20, 35 per cent. of the SP 10, and 52 per cent. of the SP 5 patients had developed streptomycin-resistant strains; these differences were not reflected in the outcome over the five-year period.

The outcome of the disease was less favourable in patients who had extensive cavitation, high pyrexia, or a high erythrocyte sedimentation rate, on admission

to the trial. It was also less favourable in patients who failed to improve radiographically, who remained bacteriologically positive, or in whom the temperature or sedimentation rate failed to respond at the end of three months.

The five-year progress of the 42 patients initially treated with streptomycin plus PAS (sodium) 20 g. in this trial was closely similar to that of the 53 like patients treated similarly, one year earlier, in the second Medical Research Council trial.

The patients in this third trial all started treatment more than seven years ago, and, judged by present standards, they were inadequately treated. The long-term efficacy of present treatment, however, can only be assessed in comparison with the long-term findings in series such as that reported here.

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# RACEMOSE ANGIOMA OF THE SPINAL CORD[1]

By M. J. D. NEWMAN

(From the Department of Neurology, Manchester Royal Infirmary)

With Plates 11 and 12

Angiomatous malformations are well known as an unusual type of spinal cord lesion. Until recently they were generally considered as chance surgical or necropsy findings, but the increasing use of myelography has led to the diagnosis of many more cases. Turner and Kernohan (1941) and Wyburn-Mason (1943) have described the various types of angioma to be found in the spinal cord. The present survey deals only with intradural racemose angioma, which is the most frequent type found in the central nervous system and also of the most clinical interest. The pathology of these lesions has been well described by Brion, Netsky, and Zimmermann (1952), as well as by earlier authors such as Brasch (1900) and Balck (1900). They vary from a fairly localized collection of large vessels, extending from the pia into the spinal cord, to very diffuse lesions characterized by proliferation of small vessels, mainly in the grey matter of the cord, and of dilated and thickened pial veins over many segments. The majority of cases appear to be of the latter type, as was the only one in the present series in which the histology was studied; it is not, however, true to say that this lesion is a purely venous angioma, as some cases with typical pathological appearances have shown oxygenated blood and pulsation in the pial veins at operation (Haberland, 1950). It is not certain that all such lesions are developmental in origin. As half the cases in the present series were diagnosed radiographically, the distinction between venous and arteriovenous could not always be made. Histologically, the abnormal veins and arteries in these malformations are often impossible to distinguish, as Bergstrand (1936) has pointed out. It is doubtful whether the colour and pulsation of the vessels at operation are a very good indication of the internal vascular connexions, and the appellation venous or arteriovenous is probably only a rough estimate of the relative size of the vessels entering and leaving. It will be shown that there is no real dichotomy of clinical features.

Nineteen cases of racemose angioma were seen in the Departments of Neurology and Neurosurgery at the Manchester Royal Infirmary between the years 1946 and 1956. During the same period 121 primary spinal tumours were seen, one case of haemangioblastoma, and four of extradural angioma. This high incidence may be contrasted with only two cases seen in the previous decade,

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as against 107 of primary tumour. In view of the changes in the type of cases recognized with new methods of diagnosis, it may be worth while reviewing the clinical features of the 19 cases mentioned above, with the additional purpose of showing whether the condition has not some place in clinical diagnosis other than as an occasional oddity.

### *Age and Sex Incidence* (Table I)

The onset of symptoms may occur at any age, but is most common in the fourth and fifth decades. One patient (Case 3) was only one year old when weakness of the legs was first noticed, and is the youngest recorded. Another (Case 19) was paraplegic from birth, but this may have been due to a separate congenital lesion, and the sciatic pain which brought him to hospital began at the age of 46. As in other reports, there was a marked predominance of male patients: 17, as opposed to only two female patients. It will be seen from the Table that arteriovenous and apparently venous angiomata have much the same age and sex distribution.

TABLE I

*Age and Sex Incidence*

Compiled from 172 published cases and the present series.

| | *Age at onset (years)* | | | | *Sex* | |
|---|---|---|---|---|---|---|
| | *0–19* | *20–39* | *40–59* | *60 and over* | *Male* | *Female* |
| Arteriovenous . . | 17 | 19 | 22 | 3 | 46 | 15 |
| Type undetermined . | 9 | 14 | 17 | 2 | 30 | 12 |
| Venous . . . . | 11 | 32 | 36 | 9 | 67 | 21 |

### *Natural History*

Once seriously disabling symptoms occur, lesions of this type usually progress more or less rapidly to complete cord transection. Eleven of the 19 patients became completely unable to walk within a period ranging from six months to four years after first noticing weakness of the legs, the average duration being just over two years. Five other patients were still able to walk, though severely disabled, after one and a half to four and a half years. But, before this phase of progressive paraplegia, a number of patients had intermittent attacks of root pain for considerable periods. A man of 59 (Case 4) had attacks of sciatica for 20 years before he noticed any weakness of the legs; a year after this he was completely paraplegic. A woman aged 54 (Case 8) had intermittent backache, with pain radiating down the front of both thighs, for 15 years, after haemorrhoidectomy under spinal anaesthesia; five years before she was admitted to the Manchester Royal Infirmary she began to have weakness of the legs, and in two years became paraplegic. A man of 45 (Case 2) had root pain, without other symptoms; in 1942 he suffered from pain in the loin, diagnosed as due to renal stones; 10 years later, after kicking a ball, he had severe abdominal pain, and

in 1954, after falling from a ladder, pain radiating from the loins to both sides of the upper abdomen. That year, and again 18 months later, the only abnormal sign to be found was tenderness of the fourth and fifth thoracic spines. In addition, one patient had transient attacks of urgency of micturition and defaecation for six months before any permanent impairment was noticed; five of the patients had shorter prodromal periods of lumbar or sacral root pain, ranging from two months to three years. It will be seen that root pain is often the first symptom. Altogether, it was present in 12 of the 19 cases in this series; in one (Case 12) it was severe enough to require cordotomy, but in the majority it became less severe as motor symptoms developed. The frequency of this symptom is explained by the large vessels which can be seen at operation running alongside the dorsal roots; histologically, abnormal vessels are often found ramifying in the substance of the spinal roots.

The phase of deterioration was in most cases steadily progressive, and a significant remission occurred only in Case 16:

A woman of 35 developed left sciatic pain in the eighth month of her third pregnancy, and this was followed a few weeks later by sudden paraplegia. She was delivered at term, and four months later she began to improve, and enjoyed a complete remission, apart from occasional pain, for two years; then again she developed incontinence of urine and paraparesis, this time of gradual onset. Radiography later demonstrated angioma of the body of the third lumbar vertebra, as well as an intradural vascular malformation (Plate 11, Fig. 1).

Relapse and remission of symptoms in relation to pregnancy has been reported in the case of vertebral angioma by Guthkelch (1948) and Newman (1958), and in intradural angioma by Girard and Garde (1955) and Delmas-Marsalet (1941). Three other patients in the present series had periods of improvement in walking, but lasting only a few months; one had retention of urine for two short periods, with subsequent relief. Sudden exacerbation of symptoms may also occur. In some cases it is due to haemorrhage, as in the cases described by Henson and Croft (1956). Spinal subarachnoid haemorrhage has been reported in 17 out of 150 cases published with full details, and racemose angioma is probably its most frequent cause. Often haemorrhage was the presenting symptom, but, in the only case in the present series in which it occurred (Case 9), it was late in the course of the disease, when the patient had been paraplegic for many years. Extensive haematomyelia is rare, but has been reported by Sterling and Jachimowicz (1937), and in association with subarachnoid haemorrhage in two of Wyburn-Mason's cases (1943). Other sudden episodes occur without obvious haemorrhage: one patient (Case 4) had suffered from only slight weakness of the legs for six months, when he woke one morning to find them completely paralysed. A similar episode has been described above in Case 16. Infarction of the cord may well be responsible in such cases. Ischaemia, in fact, is probably the most important cause of symptoms in racemose angioma. Histological sections have usually shown widespread obliteration of the smallest vessels in the affected areas, due to hyaline thickening of the intima; these changes may be caused by increased venous pressure.

*Physical Signs*

With racemose angioma of the spinal cord it is unusual to find other haemangiomata outside the central nervous system. Segmental angiomata of the skin were reported by Cobb (1915), Wyburn-Mason (1943; Case 6), Silverman (1945), Cross (1947), Gilbert (1952), and Henson and Croft (1956; Case 2): a total of six out of over 150 recorded cases. Segmental pigmented naevi were reported by Wyburn-Mason (1943; Case 29) and Ford (1944), and one occurred in a case of extradural racemose angioma seen at the Manchester Royal Infirmary. There were no segmental naevi of any type in the present series of cases. In Case 5 of Kraus (1943) a spinal racemose angioma was associated with angioma of the retina, and one patient in the present series (Case 16) had both vertebral and intradural angioma, an association which has also been reported by Girard and Garde (1955) and by Roger, Paillas, Bonnal, and Vigoureux (1951).

The neurological signs naturally depend to a large extent on the level of the lesion, but at any level may have features which depend on considerable longitudinal extent of the angioma and patchy affection of long tracts, anterior horns, and spinal roots. Such signs often distinguish them from other causes of cord compression.

The cervical region has been involved in only about one-sixth of the recorded cases. Most of the lesions affect the lower segments chiefly or exclusively, but a few, such as that reported by Cross (1947), have even extended up through the foramen magnum. Cervical cord angiomata usually show an obvious arterial element at operation, but some have appeared purely venous, such as that described by Ransome and Meckie (1941). A high proportion of cases (eight out of 27) has been detected owing to subarachnoid haemorrhage. In the present series the angioma in only one patient (Case 1) was mainly cervical in site. He was a man of 45, who complained of gradually progressive weakness of the left leg, followed after six months by retention of urine which remitted, relapsed, and remitted again. Later he noticed a sensation of coldness of the right arm. On examination there was no weakness or objective sensory loss in the upper limbs, but tendon reflexes were less brisk on the right; both legs were spastic, all abdominal reflexes were absent, and both plantars extensor; sensory loss was confined to impairment of vibration sense in the right leg. Two years after the onset of symptoms he was still able to work; there was impairment of touch and pain sensation up to the knees, but position sense was retained. Radiographic abnormalities in this case extended between the fourth cervical and fourth thoracic vertebrae, and the physical signs were mainly those of involvement of descending tracts. Other cases of cervical cord angioma have shown either quadriplegia from involvement of upper cervical segments, or some focal weakness and wasting in the upper limbs.

In 12 cases of the present series the thoracic segments were involved, with the production, most frequently, of a spastic weakness of the legs as the principal physical sign. In many of these cases it was evident that the lesion extended up into the cervical or down into the lumbar segments as well; in only

two was the lesion apparently confined to the thoracic region of the spinal cord:

*Case 2.* The patient, whose symptoms of thoracic root pain have been described on pp. 98–99, had no abnormal physical signs. *Case 3* was that of a child of 15 months, whose parents had noted increasing scoliosis and weakness of the legs from the age of one year; he had a spastic paraplegia with brisk reflexes in the legs, extensor plantar responses, and sensory loss up to the xiphisternum.

Four patients had evidence of lower-motor-neurone involvement in both upper and lower limbs, although in the former it was never gross, indicating that the lesion probably extended almost the whole length of the spinal cord:

*Case 4.* A man of 59 had suffered from left-sided sciatica for 20 years; a year before admission to hospital he had transient weakness of the left arm, and later sudden paralysis of the legs. He was found to have flaccid paraplegia, with wasting and absence of all reflexes in the lower limbs; sensory impairment to pain alone extended up to the xiphisternum.

*Case 5.* A man of 49 had a history of six months' aching and weakness of the legs and a burning feeling in the right buttock. Tendon reflexes were brisker in the right arm than in the left, and the right knee-jerk and both ankle-jerks were absent; all abdominal reflexes were absent, and both plantar responses extensor. Only vibration sense was impaired in the legs. At this stage he was still able to walk, but two years later, after a laminectomy, his legs became extremely weak, and sensory loss to pin-prick extended up to the fifth thoracic dermatome. On the myelogram abnormal vessels extended from opposite the middle cervical vertebrae to the lower thoracic region (Plate 11, Fig. 2).

In the two following cases the full extent of the lesion became apparent only at a later stage:

*Case 6.* A man of 61 complained of increasing weakness of the right leg for two years, with some pain in the thighs. On examination there was spastic weakness of both legs; tendon reflexes were depressed in the left arm, and brisk in both legs; all abdominal reflexes were absent, and both plantar responses extensor. There was sensory impairment to all modalities on both legs. Later in the same year the paraplegia became flaccid, and the tendon reflexes in the legs absent. The level of sensory loss had risen to the umbilicus. Histological abnormalities (Plate 12, Fig. 3) extended from the cervical enlargement to the lumbar segments of the cord.

*Case 7.* A man of 57 complained of pain in the right foot, followed by weakness of both legs. On examination the knees were spastic, with brisk knee-jerks, but the ankles were flaccid, with absent jerks. The lower abdominal reflexes were absent, and both plantars extensor. Sensory impairment extended up to the groins, with sacral sparing. Four years later the legs were entirely flaccid, and all reflex activity in them had disappeared; in the arms, tendon reflexes were brisker on the right than on the left. The sensory level had not changed, but the loss was more complete.

The progression, exemplified by three of the above four cases and Case 9, from spastic to flaccid paraplegia, with ascending sensory loss, was put forward as a characteristic feature of subacute necrotic myelitis by Foix and Alajouanine (1926), whose cases are now generally considered to be examples of

racemose angioma. Three of the above patients had an obviously arteriovenous malformation at operation, but in Case 6 the histological picture was that of a so-called venous angioma.

The remaining six cases involving the thoracic cord presented a mixture of spastic and flaccid weakness of the legs, indicating patchy involvement of the lower thoracic and lumbar segments. In particular, the combination of absent ankle-jerks with extensor plantar responses was found in many patients:

*Case 8.* A woman of 54 had a long history of lumbar root pain, followed after 10 years by progressive weakness of the legs. When seen in 1954 she was paraplegic, the right leg being spastic with increased tendon reflexes, and the left wasted with absent tendon reflexes; both plantar responses were extensor, and sensory loss to all modalities was present up to the fifth thoracic segment. Radiographically the angioma extended from the lower cervical region at least as far as the 10th thoracic vertebra.

*Case 9.* A boy of nine years complained of weakness of his left leg for two years, during which period he had had one temporary remission. The leg was weak, with wasting of the glutei; tendon reflexes were all present, the lower abdominal reflexes were absent, and both plantar responses were extensor. No sensory loss was detected. Two years later both legs became paralysed, and sensory loss extended up to the seventh thoracic segment. After 10 years there was very little change in the physical signs, except that tendon reflexes in the arms had become very brisk. It was at this time that he had the subarachnoid haemorrhage mentioned on page 99.

*Case 10.* A man of 56 had a year's history of sciatic pain, followed by weakness of the left leg. The quadriceps on this side was spastic, and the knee-jerk very brisk, but both ankle-jerks were sluggish, and there was wasting of the left glutei, hamstrings, and calf muscles. The lower abdominal reflexes were absent, both plantar responses were extensor, and there was sensory impairment to all modalities up to the umbilicus.

*Case 11.* A man of 67 suffered from ankylosing spondylitis, and complained of weakness of the legs for a year. There was flaccid weakness of the legs, with generalized wasting; the knee-jerks were sluggish, ankle-jerks absent, all abdominal reflexes absent, and both plantar responses extensor. Sensory impairment to pain, more than to light touch, extended to just above the groins.

*Case 12.* A man of 62 had a five years' history of rectal pain eased by lying down, followed by hesitancy of micturition, and then by weakness of the legs. He had a flaccid paraplegia, with generalized wasting; all the abdominal reflexes were absent, the knee-jerks sluggish, ankle-jerks absent, and plantar responses extensor. Dense sensory loss extended up to the groins, but postural sensation was retained in the right foot. Although the physical signs were very similar to those of the previous case, and seemed to indicate predominantly lumbar cord involvement, an operation for cordotomy at the level of the third and fourth thoracic vertebrae revealed abnormal pial vessels at this level as well as lower down.

*Case 13.* A man of 67 gave a history of pain in the right leg, followed by weakness. Both legs were weak and spastic, with brisk knee-jerks but absent

ankle-jerks; the lower abdominal reflexes were depressed, and both plantar responses extensor. There was impairment of sensation to pin-prick alone over the sacral segments.

Four of these six patients were operated upon, and the angioma appeared to be venous in three and arteriovenous in one (Case 12). The physical signs in the above 12 cases are summarized in Table II.

TABLE II

*Physical Signs in Angiomata of the Thoracic Cord*

| *Case number* | *Type of angioma* | *Myelographic (vertebral) level* | | *Abnormal signs in upper limbs* | *Abdominal reflexes* | *Abnormal signs in lower limbs* | | | *Level of sensory loss* |
|---|---|---|---|---|---|---|---|---|---|
| | | *Upper* | *Lower* | | | *Wasting* | *Tendon reflexes* | *Plantar responses* | |
| 2 | .. | T 1 | T 9 | Nil | Present | Nil | Normal | Flexor | Nil |
| 3 | Arteriovenous | T 6 | T 12 | Nil | Absent | Nil | Brisk | Extensor | T 8 |
| 4 | Arteriovenous | .. | T 11 | Symptoms only | Absent | Both legs | Absent | Absent | T 8 |
| 5 | Arteriovenous | C 5 | T 10 | Tendon reflexes depressed L. arm | Absent | R. leg | Absent except L. knee-jerk | Extensor | T 5 |
| 6 | Venous .. | C 5 | T 12 | L. triceps-jerk depressed | Absent | Nil | Present; later absent | Extensor | L 3 |
| 7 | Arteriovenous | T 10 | L 1 | Tendon reflexes depressed L. arm | Lower absent | Nil | Ankle-jerk absent | Extensor | T 12 |
| 8 | .. | C 7 | T 10 | Nil | Absent | L. leg | Absent L. leg | Extensor | T 5 |
| 9 | Venous .. | T 6 | L 1 | Nil | Lower absent | L. glutei | Ankle-jerks absent | Extensor | T 7 |
| 10 | Venous .. | T 7 | T 12 | Nil | Lower absent | L. leg | L. knee-jerk brisk | Equivocal | T 10 |
| 11 | Venous .. | .. | .. | Nil | Absent | Both legs | Absent | Extensor | T 11 |
| 12 | Arteriovenous | .. | T 10 | Nil | Absent | Both legs | Ankle-jerk absent | Extensor | L 1 |
| 13 | .. | T 9 | L 1 | Nil | Lower absent | Nil | Ankle-jerk absent | Extensor | S 2 |

The remaining six patients had lesions which, when they were first seen, affected only the lumbar segments and the cauda equina. In Cases 11 and 19 signs later appeared indicating upward extension, and in Case 16 the abdominal reflexes were all absent, although there was no other evidence of a lesion above the lumbar cord.

*Case 14.* A man of 42 was referred to the Department of Neuroradiology at the Manchester Royal Infirmary for a second opinion on a myelogram already performed. He had had hesitancy of micturition for two years, followed by weakness of the legs which was very variable from day to day. The weakness was mainly in the left leg, and the left knee-jerk and both ankle-jerks were depressed; the plantar responses were not obtainable. There was impairment of sensation to pin-prick over the sacral segments.

*Case 15.* A man of 59 had a two years' history of left-sided sciatica, followed by weakness of the left leg. There was weakness and some wasting of the left leg, with depressed knee- and ankle-jerks on this side, and absent plantar responses. There was sensory impairment to all modalities on the left below the groin.

The history in *Case 16* has been described on page 99. When the patient was seen just after the relapse of symptoms, her left leg was weak, both knee-jerks

were brisk, the ankle-jerks absent, and plantar responses flexor. There was some sacral sensory loss on the left side. A year later there was flaccid paralysis of the left leg, but good power in the right, although all reflexes in the legs, and the lower abdominal reflexes, were now absent, and sensory impairment extended above the umbilicus.

The above three patients had markedly asymmetrical symptoms and signs; the following three cases were more symmetrical.

*Case 17.* A man of 54 complained of pain down the front of the thighs for two years, followed by fairly sudden paralysis of the legs. There was a considerable remission, so that he was able to walk again for some months, but he again relapsed, and was found to have flaccid paraplegia, with absence of all reflexes in the legs as well as of all abdominal reflexes. Sensory loss to all modalities extended up to the groins.

*Case 18.* A man of 49 was first seen with a history of intermittent attacks of sudden weakness of the legs, with urgency of bowel and bladder action. No abnormal physical signs were found apart from depression of the left ankle-jerk. Three years later, however, there was marked weakness and wasting of both legs; the knee-jerks were sluggish, ankle-jerks absent, both plantar responses extensor, and the lower abdominal reflexes absent; slight impairment of sensation extended above the umbilicus.

*Case 19* should be classed separately; the patient was a man who had been paraplegic from birth, and had complete atrophy and paralysis of the legs, with apparently normal sensory function (the fact that he spoke only Welsh made sensory testing difficult). All reflexes in the legs were absent; the abdominal reflexes were present, but the cremasteric reflexes absent. It is possible that the paralysis was the result of a congenital abnormality, separate from the angioma, which was demonstrated radiographically.

Only three of the patients with lumbar lesions came to operation, and in all three the angioma appeared to be arteriovenous.

### *Investigation*

In every case in this series the cerebrospinal fluid was abnormal. A complete manometric block was found in three cases, and a partial block in two others. In all these five cases the protein content was raised. In the remaining 13, without any block, the protein was increased to between 50 mg. and 300 mg. per 100 ml. The cell count was normal except in one patient (Case 2), who had 22 lymphocytes per cu. mm. In other published cases the cerebrospinal fluid has not always been abnormal; out of 76 patients in whom the protein content was estimated, it was 55 mg. per 100 ml. or more in 59 (78 per cent.), ranging as high as 350 mg. per 100 ml. even in the absence of a block.

Plain radiography of the vertebral column seldom shows any abnormality. The vertebral angioma in Case 16 has been mentioned; in Case 13 there was a wedge deformity of the ninth thoracic vertebra, possibly due to an old crush fracture. The characteristic pattern produced by intrathecal radio-opaque oils in these lesions was first described by Guillain (1925); the tortuous dilated

vessels on the pia give rise to curved filling defects, such as those seen in Plate 11, Fig. 2, and Plate 12, Fig. 4. A similar picture has been described in at least 36 cases, apart from those reported here, and the diagnosis was confirmed at operation or necropsy in 31. No case appears to have been reported in which such filling defects have been proved due to any other condition. The irregular filling defects found in adhesive arachnoiditis can readily be distinguished, but small curved vascular shadows can sometimes be seen above a complete block due to an intradural tumour. Myelography was performed in 18 cases in the present series, and a typical appearance was seen in 14. Case 14 showed only a single curved filling defect, but an extensive angioma was found at operation. In two cases a complete block was seen, and in one a partial block, without vascular shadows, and the diagnosis was made at operation. It seems probable that a diagnostic myelographic appearance can be found in three-quarters of cases of racemose angioma.

Vertebral angiography was performed by Henson and Croft (1956) in Case 2 of their series, and demonstrated an upper cervical arteriovenous angioma; it is unlikely that aortography would be of any value in lesions lower down the cord, on account of dilution of the dye.

### *Diagnosis*

Undoubtedly the most important distinction remains that from benign tumours pressing on the spinal cord, for the reason that these are often amenable to surgical treatment. From a clinical standpoint an angioma producing signs only of a localized lesion, such as Case 3 in the thoracic region or Cases 14, 15, and 17 in the lumbar region, may resemble a spinal tumour very closely in both physical signs and symptoms, and the distinction could only be made by myelography or at operation. In Case 1, although some remission of symptoms occurred, and although there was little sensory loss, the signs were compatible with a localized compressive lesion. In such cases with a remittent history the alternative diagnosis of disseminated sclerosis must be considered. When the physical signs make it apparent that the lesion extends over the greater part of the spinal cord, as in Cases 4, 5, and 6, the distinction from a single compressive lesion is very clear. The diagnosis must lie between angioma and multiple tumours or a combination of lesions, such as cervical spondylosis and a separate lumbar cord affection; rarely a syringomyelic cavity may extend to the lower end of the cord.

Perhaps the most characteristic group of physical signs among the patients in the present series was the presence of spastic weakness of some muscles in the legs and extensor plantar responses, combined with wasting of other muscles and absence of certain tendon reflexes, as in Cases 8 to 13. Such muscular wasting and disappearance of reflexes may occur in other cases of spastic paralysis, but, except in the acute phase, usually only when there is long-standing paraplegia in flexion. This condition was not found in any of the patients here described. Some intramedullary tumours may extend over a

considerable length of the spinal cord and produce such a picture, as may multiple disk protrusions; the frequency of sciatic pain is another point of resemblance to intervertebral disk lesions. When the signs are symmetrical, the features may be similar to those seen in cases of myeloneuropathy due to carcinoma, to polyarteritis, or to unknown causes; the type described in diabetics by Garland and Taverner (1953) resembles some of the cases in the present series, even to the changes in the cerebrospinal fluid. The same type of clinical picture is also described in cases of subacute necrotic myelitis not due to angioma, such as those of Davison and Brock (1944); a case of this type due to spinal thrombophlebitis has been described by Mair and Folkerts (1953). In spite of these differences from the usual picture of spinal cord compression, it is not in many cases of angioma that the diagnosis could be made with sufficient assurance to dispense with a myelogram. When this investigation shows only a block in the subarachnoid space, even if pulsation or a few curved vascular shadows are seen, exploratory laminectomy must be undertaken in case a curable condition should be overlooked.

### *Treatment*

British neurosurgeons on the whole (Sargent, 1925; Wyburn-Mason, 1943) have found operation on these lesions uniformly disappointing. In not one of the 11 patients of the present series who were operated upon was any removal of the abnormal vessels feasible, nor did any marked improvement result from opening the dura mater. Two (Cases 7 and 17) were able to walk a little better after operation, but their improvement might well be attributed to physiotherapy; both had deteriorated again in a few months. One patient (Case 5) was considerably worse after operation, and another (Case 15) developed sudden and complete paraplegia. Some surgeons have tried to ligate or coagulate the abnormal blood-vessels, and in a few cases have been able to secure considerable amelioration of symptoms. A total of seven patients were markedly improved: Cases 1, 7, and 8 of Bassett, Peet, and Holt (1949), Cases 2 and 3 of Puusepp (1938), Case 1 of Hackel (1929), and Case 23 of Trupp and Sachs (1948). The last case was that of a boy of 10 years, who developed sudden paraplegia; a huge pulsating vessel at the upper end of the lumbar enlargement was coagulated, and he recovered and two years later could walk well. The other patients all had root pain, but little weakness and minimal physical signs. The period of follow-up was not longer than a year, and it is not certain whether the progress of the symptoms was halted or merely delayed. Operative treatment is not likely to be successful in a case with progressive motor impairment, or when physical signs or the myelogram indicate that the angioma involves a great length of the spinal cord. Laminectomy with simple decompression confers no benefit; out of 67 records of this operation, seven patients were slightly and temporarily improved, 31 were unchanged, and 29 became worse or died. Unless the diagnosis is uncertain, or the angioma appears to be localized and no irreversible damage has been done to the spinal cord, operation should be

avoided. Radiotherapy was given alone or after operation in 30 cases, and two significant remissions occurred; both these patients (Case 6 of Insausti (1951) and Case 2 of Henson and Croft (1956)) had come to notice with subarachnoid haemorrhage, after which spontaneous remission may occur.

Even if surgery is usually inadvisable or of no avail, conservative treatment is not always unrewarding. One patient (Case 7), although completely paralysed below the waist, had not missed a day's work through illness in three years. When paraplegia occurs the patient is usually relieved of his root pain, and the upper limbs remain unaffected. Unfortunately the shortage of beds in special paraplegic centres makes the rehabilitation of such patients often difficult. It should be mentioned that a patient first seen with this condition in 1932, and paraplegic since 1940, had in 1956 developed weakness and paraesthesia in the right hand, so that it is possible that slow upward extension of the lesion can occur.

I am grateful to Sir Geoffrey Jefferson, Dr. F. R. Ferguson, Dr. G. E. Smyth, and Mr. R. T. Johnson for allowing me to study patients under their care, and to Mr. F. Mercer and the Department of Neuroradiology at the Manchester Royal Infirmary for the myelograms; also to Dr. E. C. Hutchinson for much helpful advice and criticism.

*Summary*

A review has been undertaken of 19 cases of racemose angioma of the spinal cord, and their principal clinical features described. Three of the patients had a long prodromal period of root pain for a number of years before other symptoms occurred. Root pain was a prominent feature in 12 of the 19 patients. In other respects the course of the disease was usually one of progressive deterioration; a major remission occurred in only one case, and minor remissions in five. Subarachnoid haemorrhage occurred in one patient, but is reported in 10 per cent. of published cases.

The neurological signs are described. Segmental skin naevi were not seen, but are reported in 5 per cent. of published cases. Signs of a lesion extending from the cervical to the lumbar region of the cord were present initially in two cases, and later in two others. Six patients had evidence of a thoracic cord lesion extending down into the lumbar enlargement, typically with a combination of spastic paralysis and absent tendon reflexes in the legs; two other patients later developed a similar condition.

Cerebrospinal-fluid protein was increased in all cases, although a manometric block was present in only five. A diagnostic myelographic appearance was seen in 14 out of 18 cases.

The clinical picture is characteristic, and distinct from that of spinal tumour, in about half the cases.

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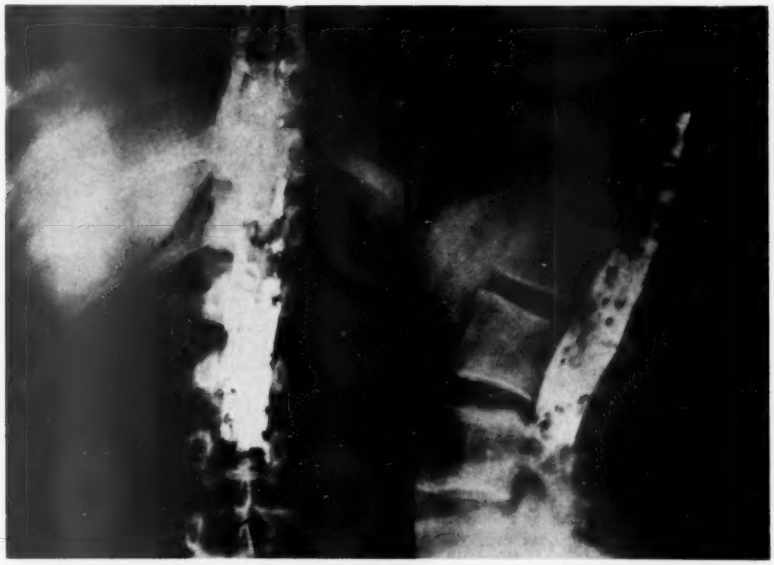

FIG. 1. Myelogram in Case 16, to show the typical appearance of an angioma of the body of the third lumbar vertebra in addition to the filling defects of an intradural angioma. (By courtesy of the *Journal of Neurology, Neurosurgery and Psychiatry*)

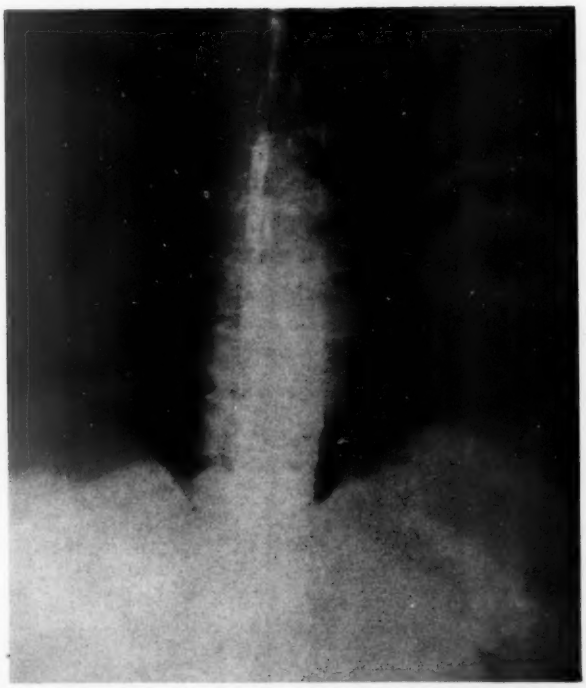

FIG. 2. Myelogram in Case 5, to show vascular shadows extending the whole length of the thoracic region

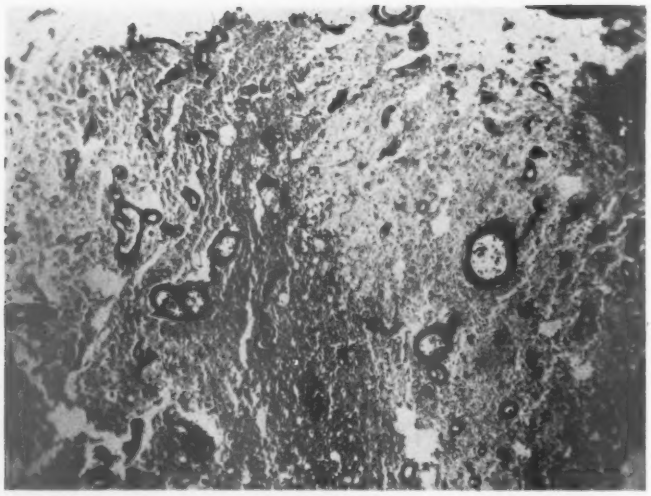

FIG. 3. Section of the spinal cord in Case 6, showing numerous abnormal arterioles and capillaries in the region of the posterior columns (haematoxylin and van Gieson, × 80)

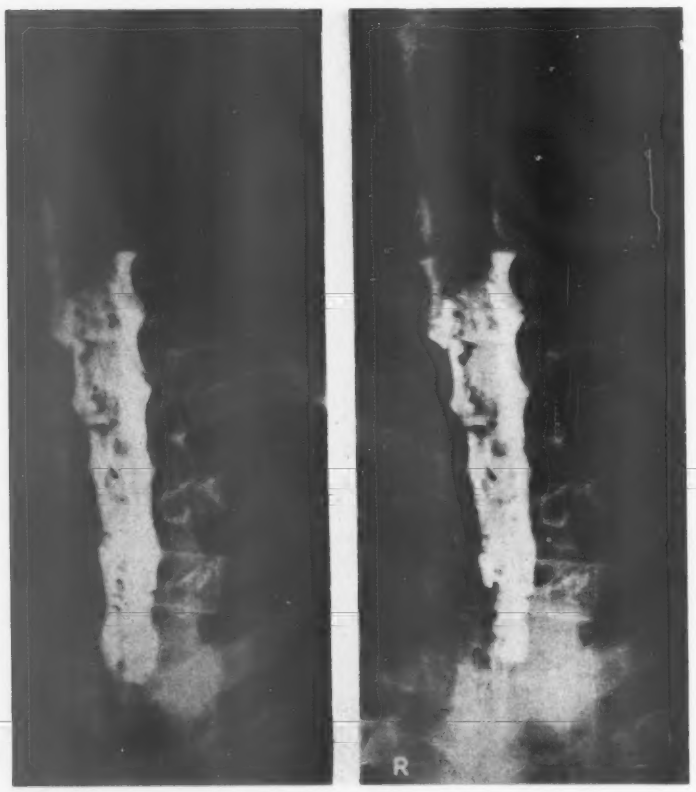


FIG. 4. Myelogram in Case 1. Abnormal vessels in the lower cervical region

616.5–002.71

# DERMATOLOGICAL ASPECTS OF SARCOIDOSIS[1]

By D. GERAINT JAMES

(From The Institute of Clinical Research, The Middlesex Hospital Medical School)

With Plates 13 to 15

## *Historical*

In the years preceding and following 1900 several publications independently drew attention to what we now regard as sarcoidosis. Depending on the authors' interests, they separately described skin lesions, bone cysts, parotid and eye involvement, and lymphadenopathy. The diversity of tissues involved was matched only by the variety of synonyms invoked by the authors, who were unaware of the essential unity of the various manifestations of the disease. Furthermore, dermatologists among themselves were uncertain whether their published examples were related to previously reported, and even illustrated, descriptions by others. In this way confusion grew, and both synonyms and eponyms have multiplied to a score. The historical background well illustrates the protean clinical manifestations of sarcoidosis.

The first recorded and illustrated example is attributed to Hutchinson (1877). His patient, John W—, was a florid man of 58 years working at a coal-wharf. He came under Hutchinson's care at the Hospital for Skin Diseases in January 1869, and remained under his observation for one year. Hutchinson considered that the skin lesions were in some way related to the patient's gout. In a much later publication 'On eruptions which occur in connection with gout', Hutchinson (1898) recalled this first example with the remark, '. . . He had suffered from gout, and he finally died of contracted kidneys. I was inclined to consider the skin-disease as essentially connected with gout. . . .' John W— died in 1875 from kidney disease after treatment at King's College Hospital. It is now recognized that patients with sarcoidosis occasionally have disordered calcium metabolism, leading to renal calculi and terminal renal failure. It is interesting to speculate whether John W—'s skin lesions and terminal renal disease were interrelated. In the summer of 1869 Hutchinson visited Christiania, where Dr. Bidenkap showed him a pathological drawing of a patient of Professor Boeck, illustrating skin lesions precisely similar to those of John W—. This Professor Carl William Boeck (1808–75) was an uncle of Caesar Boeck (1845–1917), who was later to make valuable contributions to the study of sarcoidosis. Both occupied the professorial chair at Christiania, separated in its tenure by the

[1] Received March 12, 1958.

Dr. Bidenkap who had been Hutchinson's guide. In 1889 Besnier described a patient with violaceous swellings of the nose, ears, and fingers, for which he coined the term lupus pernio. He referred to Hutchinson's patient, John W—, but the distribution of the lesions was sufficiently dissimilar to justify his opinion that the two conditions were not identical. Tenneson (1892) reported another example of lupus pernio, and added the essential histological description of 'predominance of epithelioid cells and a variety of giant cells' in the skin lesions.

Hutchinson had by 1898 observed another two examples, and he likewise considered the disease to belong to the lupus family, for he recorded: 'I have to describe a form of skin disease which has, I believe, hitherto escaped special recognition. It may not improbably be a tuberculous affection and one of the lupus family, but if so it differs widely from all other forms of lupus, both in its features and its course. . . . The disease is characterised by the formation of multiple raised, dusky-red patches which have no tendency to inflame or ulcerate. They are very persistent, and extend but slowly. They occur in groups and are usually on both sides and almost symmetrical. The multiplicity of the patches, their occurrence in groups, their bilateral symmetry, and the absence of all tendency to ulcerate or form crusts, are features which separate the malady from lupus vulgaris. To none of the other forms of lupus has the malady any resemblance. The malady might perhaps be named Lupus Vulgaris Multiplex non-ulcerans, but for the present I prefer to recognise it, by the name of one of its subjects, as Mortimer's Malady.' Mrs. Mortimer was aged 64 years when she developed these lesions. Hutchinson presented her to a meeting of the Dermatological Society of London in 1895, when the consensus of opinion favoured the diagnosis of sarcoma, and urged skin biopsy for histological proof. Hutchinson subsequently suggested this course of action to Mrs. Mortimer, with the result that he did not see her again for two years.

By this time Caesar Boeck had succeeded Bidenkap to the professorship at Christiania, and in 1899 recorded his example of 'Multiple benign sarkoid of the skin', and drew attention to its similarity to Mortimer's malady (Boeck, 1899*a*, *b*). Boeck's patient was a man of 36, who had developed several skin patches in the course of years, and in addition had lymphadenopathy, particularly of the epitrochlear glands. Unlike Hutchinson, Boeck was fortunately able to study the skin histologically, and noted the sharply defined foci of epithelioid cells, with some giant cells, permeating the corium. The lymph-nodes were not examined. The conclusion to his first communication was that the condition might prove to be connected with the pseudoleukaemias, but subsequently Boeck amended this view in favour of a generalized disorder allied in some way to tuberculosis. Further reports drew attention to bone cysts, which Kienböck (1902) connected with syphilis, and Kreibich (1904) with lupus pernio, and which Jüngling (1920–1) called 'ostitis tuberculosa multiplex cystica'. Heerfordt (1909) described uveo-parotid fever, and Kuznitzky and Bittorf (1915) drew attention to the pulmonary manifestations of sarcoidosis. At this stage a pathological synthesis of the diverse aspects of the disease was due, and was

offered in an admirable prize essay by Schaumann (1917), who distinguished the condition from Hodgkin's malignant granuloma by calling it *lymphogranulome benin*.

The suggestion that erythema nodosum with bilateral hilar lymphadenopathy may be caused by sarcoidosis is more recent. In 1942 Kerley recorded 12 young adults with this association, eight of whom developed sarcoid-like infiltration of the lungs. Lofgren (1946) analysed 178 cases of erythema nodosum, and found 15 in which sarcoidosis was probable despite lack of histological proof. In a further Swedish survey, in 1953, he obtained histological proof of sarcoid tissue in one-quarter of a series of 113 patients with erythema nodosum and bilateral hilar lymphadenopathy. In Great Britain histological proof of sarcoidosis was obtained in 27 patients with this syndrome (James, Thomson, and Willcox, 1956). From this series it was not possible to define how often erythema nodosum was due to sarcoidosis, but the association should particularly be looked for in young adult women. This predilection of erythema nodosum for female patients had already been clearly recorded by Willan in his original description (1808). Physicians 150 years later are still undecided about its pathogenesis and confused as to the relative frequency of its different causes, and have no better treatment than the Peruvian bark advocated by Willan.

### *Patients Investigated and Methods*

The 200 patients studied showed clinical or radiological features of sarcoidosis, supported by histological evidence of sarcoid tissue. Patients with clinical, radiological, and immunological features of sarcoidosis have been excluded if there was no histological confirmation. The series includes 33 patients (16·5 per cent.) with various skin lesions (Table I), and a further 62 patients (31 per cent.) with erythema nodosum. The remaining 105 patients showed no skin involvement; they are occasionally referred to as the 'non-skin group'. In addition, attention is drawn to a group of 10 patients in whom histological evidence of cutaneous sarcoid tissue is unaccompanied by any evidence of the generalized disease. These lesions are termed local sarcoid-tissue reactions (Table II, page 115).

Clinical examination has been augmented by radiographs of chest, hands, and feet. Mantoux tests have been performed as a routine; 53 patients who were negative to 100 tuberculin units (1:100 old tuberculin) have been inoculated intradermally with depot tuberculin and control solution (James and Pepys, 1956). Kveim tests (Kveim, 1941; James and Thomson, 1955) have been performed in 149, and beryllium patch tests (DeNardi, Van Ordstrand, Curtis, and Zielinski, 1953; Sneddon, 1955) in 30 patients. Paper zone electrophoresis of the plasma proteins, and estimation of the serum albumin and globulin levels by the biuret method, were undertaken in 148 patients. Histological evidence of sarcoid tissue has been obtained from various sources by biopsy and at necropsy. The Hayes–Martin drill was used for skin biopsy, the specimen obtained being a core of epidermis and dermis 5 mm. in diameter. Serial

biopsies from skin, nasal mucosa, and Kveim reaction sites were done to evaluate the histological response to various forms of treatment. Sarcoid tissue is composed of well-defined spherical follicles of large epithelioid cells staining pink

TABLE I

*Involvement of Tissues in Patients with Skin Lesions*

| *Patient* | *Age at onset (years)* | *Sex* | *Tissues involved* | | | | | | *Duration (years)* |
|---|---|---|---|---|---|---|---|---|---|
| | | | *Lungs* | *Eyes* | *Lymph-nodes* | *Spleen* | *Bone* | *Others* | |
| *Lupus pernio* | | | | | | | | | |
| 1 | 50 | F | + | − | − | − | − | Nasal mucosa | 5 |
| 2 | 47 | F | + | − | − | − | + | Knee plaques | 4 |
| 3 | 25 | M | + | + | − | − | + | Parotid | 16 |
| 4 | 38 | F | + | + | + | − | − | .. | 9 |
| 5 | 66 | F | + | + | − | − | − | Tonsil, lacrimal gland | 3 |
| 6 | 40 | F | + | − | − | − | + | Knee plaques | 5 |
| 7 | 48 | F | − | − | − | − | + | Nasal mucosa | 3 |
| 8 | 35 | F | + | + | − | − | + | Palate | 8 |
| 9 | 48 | F | + | + | + | − | + | .. | 25 |
| *Persistent plaques* | | | | | | | | | |
| 10 | 60 | F | − | − | + | − | − | Bundle-branch block | 15 |
| 11 | 26 | F | + | − | − | + | − | Cor pulmonale | 3 |
| 12 | 34 | F | + | + | + | + | − | .. | 8 |
| 13 | 43 | M | − | − | + | + | − | Kidney | 2 |
| 14 | 50 | M | + | − | + | − | − | .. | 8 |
| 15 | 47 | F | + | − | + | − | − | .. | 5 |
| 16 | 46 | F | + | − | − | − | − | .. | 3 |
| 17 | 32 | M | + | − | + | − | + | .. | 5 |
| 18 | 39 | F | + | − | + | − | − | .. | 3 |
| 19 | 31 | F | + | − | + | − | − | Larynx | 5 |
| *Maculo-papular eruption* | | | | | | | | | *Months* |
| 20 | 26 | F | + | + | + | − | − | Parotid | 1 |
| 21 | 46 | F | + | + | − | − | − | Skin scar | 1 |
| 22 | 27 | F | + | − | + | − | − | .. | 1 |
| 23 | 56 | F | + | + | − | − | + | Thyroid | 24 |
| 24 | 13 | F | + | − | + | + | − | Tonsil | 3 |
| 25 | 53 | F | − | + | + | + | − | .. | 1 |
| 26 | 26 | F | + | + | + | − | − | .. | 9 |
| 27 | 45 | F | + | − | + | + | − | .. | 1 |
| *Scars* | | | | | | | | | |
| 28 | 54 | F | + | + | − | − | + | Parotid | .. |
| 29 | 43 | M | + | − | − | − | − | .. | .. |
| 30 | 38 | M | + | − | − | − | − | .. | .. |
| 31 | 42 | F | + | + | + | − | − | Parotid | .. |
| 32 | 62 | M | + | + | − | − | + | .. | .. |
| 33 | 45 | F | + | − | + | − | − | .. | .. |

with eosin, occasional giant cells, a thin peripheral ring of lymphocytes, and inconspicuous central necrosis (Plate 13, Fig. 2). Reticulin stains often reveal a persistence of fine fibrils passing through the centre of the follicle. The absence of acid-fast bacilli, caseation, or calcification also serves to distinguish it from tuberculous tissue.

### *Skin Lesions*

*Lupus pernio.* Nine patients showed involvement of the nose, cheeks, or ears by this chronic eruption (Plate 14, Fig. 3). The changes developed insidiously, progressed indolently, and were persistent. Intrathoracic changes have similarly

been associated with negligible pulmonary symptoms in the presence of extensive radiological changes (Table IV, page 117). These well-developed and obvious skin changes surprisingly proved to be a mode of presentation in but two instances, principally because of the associated sore nostrils. The remaining patients first sought medical advice because of swollen digits or ocular symptoms. Bone cysts, with overlying swelling and deformities of fingers, were troublesome in five patients, and led to amputation of a finger in one of them. Corticosteroid therapy has relieved the others without such heroic surgical measures. Uveitis was the initial presentation in two, but was present at some stage in five patients; it progressed to complete blindness in one instance. In most patients sarcoid tissue was also detected in some other tissue, including tonsil, palate, parotid or lacrimal gland, nasal mucosa, or skin lesions elsewhere (Table I). The duration of lupus pernio has ranged from three to 25 years (Table I). Only one patient (No. 8) has died, and this event followed a massive pulmonary haemorrhage. The indolence of the skin changes is mirrored by that of the lung lesions, for radiological clearing has occurred in only one patient (Table III).

*Persistent plaques.* It is probably artificial to segregate a group of 10 patients who suffered from persistent plaques (Plate 14, Fig. 4; Plate 15, Fig. 5*a*). In many instances they differed from those with lupus pernio only in location of the lesions. Nevertheless, these large purple elevated patches, often bilateral and nearly symmetrical, commonly situated on the limbs and buttocks, recall the type of lesion first recognized and described graphically by Hutchinson (1898). If there were a return to eponyms these eruptions should surely be called Hutchinson's plaques. In only three instances did patients seek medical advice because of the skin lesions. The modes of presentation in the remaining patients included breathlessness in two, cervical lymphadenopathy in two, and uveitis, a swollen finger, and a routine chest radiograph respectively in the other three. Intrathoracic involvement was similar to that seen in lupus pernio, the predominant changes being long-standing or irreversible pulmonary fibrosis. Unlike the patients with lupus pernio, this group has been virtually free of uveitis and bone cysts; but there has been a greater predilection for lymphadenopathy, and in three instances splenomegaly. Plaques have persisted for periods from two to 15 years (Table I). One patient (No. 11) has died from cor pulmonale secondary to severe pulmonary fibrosis.

*Maculo-papular eruptions.* The reason for grouping eight female patients with transient maculo-papular eruptions is that the rash appeared to herald the onset of the disease. It usually coincided with the development of troublesome uveitis, enlarged lymph-nodes in the neck, axillae, or groins, and in some instances parotid, tonsillar, or thyroid involvement. These features were sufficiently alarming and sudden in onset for the patients to seek early medical advice and investigation. The hypothesis that these eruptions are prodromal is substantiated by the chest X-ray findings, for intrathoracic involvement was at an earlier stage of development than in the patients with lupus pernio or persistent plaques. The eruption occurred at various sites, including the trunk

in four patients, the face, arms, and thighs in one, both calves in another, and the ears or fingers in each of another two patients. It disappeared permanently after one month in five patients, and after three and nine months respectively in another two; in one instance it recurred on the calves over a period of two years (Plate 15, Fig. 6). This recurrent eruption coincided with exacerbations of iridocyclitis.

*Scars.* There remains a group of six patients with generalized sarcoidosis in whom changes in skin scars drew attention to or provided histological evidence of the disease (Plate 15, Fig. 7). In five patients scars on the knees had followed trivial accidents in childhood, and one was an operation scar. In all instances these previously atrophic scars had suddenly become purple and livid, proclaiming some inflammatory change. Biopsy revealed active sarcoid tissue, as distinct from the inactive scar tissue which was observed at other times in the same areas of skin. There is no explanation for this phenomenon, in which the sarcoid process seems to creep into and activate the scars, but it suggests a hypersensitivity reaction akin to erythema nodosum. Inoculation sites may also contain sarcoid tissue. The commonest site is that of the intradermal Mantoux test, for this is repeated at frequent intervals. Although the reaction is studied two or three days later, it is rarely observed after one month, when a nodule of sarcoid tissue may have developed. Such a Kveim-like reaction occurred in three patients in this group. It is too infrequent to be adopted as a practical diagnostic test, but its occurrence is significant, since large tuberculin-testing surveys have not disclosed this phenomenon in tuberculosis or other diseases. In other respects this group of patients was not distinctive. Pulmonary involvement occurred in all, uveitis in three, and lymphadenopathy, bone cysts, or parotid involvement in two patients. In all instances intrathoracic involvement consisted of long-standing bilateral hilar lymphadenopathy and pulmonary mottling. This fact suggests that the reaction in the scars was not an initial manifestation of the disease, but an exacerbation late in its course. The phenomenon is also observed at the onset of erythema nodosum, but it is then a transient early feature, whereas in this group it was recurrent or persistent. Three of the six patients had learned to anticipate an exacerbation of iritis when their scars became livid and inflamed.

*Erythema nodosum* has been followed in 62 patients. The lesions were always present on the shins, and also on the arms in 12 instances. They persisted about two weeks, with a range from one to six weeks. Two patients had a recurrence after two months. Some constitutional disturbance was usual at the onset, with fever up 102° F. Forty patients (64 per cent.) had an associated polyarthralgia, usually involving the knees, ankles, wrists, and elbows, and movement was limited by pain. It preceded erythema nodosum in 25 and coincided with it in 15 patients. Joint effusions were not observed, and polyarthralgia always subsided without any sequel. In all but three patients erythema nodosum was associated with bilateral hilar lymphadenopathy (Table IV). The acute nodes on the shins revealed sarcoid tissue in two of 12 biopsies. At the onset of erythema nodosum careful search may reveal vesicular, papular, or herpetiform

eruptions on the hands, elbows, or trunk, or indurated plaques may develop in old scars. Biopsy of these recent lesions revealed sarcoid tissue in seven cases, and cervical lymph-node biopsy was positive in another four patients. Skin and lymph-node lesions may subside within a week, so that early biopsy is imperative. Aspiration liver biopsy revealed miliary granulomata in six of eight patients, and the Kveim test was positive in 53 of 57 patients in whom it was performed (Table X, page 119).

TABLE II

*Sarcoid Skin Reactions*

| *Patient* | *Age (years)* | *Sex* | *Mantoux test** | *Kveim test** | *Type of skin lesion* | *Precipitating factor* | *Fate* |
|---|---|---|---|---|---|---|---|
| A | 25 | M | — | — | Sebaceous cyst of scalp | .. | No recurrence after surgical repair |
| B | 36 | M | n.d. | n.d. | Red scar, bridge of nose | Car accident | |
| C | 54 | F | + | — | Cyst, naso-labial fold | .. | |
| D | 35 | F | + | — | Naevus, lobe left ear | .. | |
| E | 38 | F | + | — | Nodules of face | Car accident | |
| F | 56 | M | n.d. | n.d. | Thickened oedematous eyelid | ? Chronic infection | |
| G | 57 | F | + | n.d. | Papules, forehead and chin | .. | Spontaneous clearing |
| H | 59 | F | + | — | Vesicles, left side neck | Hodgkin's disease of skin; treated by deep X-rays | |
| I | 42 | F | + | — | Papules, face and back of hands | .. | |
| J | 43 | F | + | n.d. | Nodules, right cheek | Bomb injury | |

* n.d. = not done.

*Local sarcoid-tissue reactions.* This group of 10 patients had sarcoid tissue in the skin, but none showed any evidence of the generalized disorder (Table II). In no instance was there clinical or radiological involvement of the lungs, eyes, spleen, or bone. In one patient cervical lymphadenopathy coincided with the local facial lesion, but unfortunately cervical lymph-node biopsy was not done. The majority showed a positive Mantoux status, and the Kveim test was negative in the six patients in whom it was performed. Serum-globulin levels were normal. Thus the sarcoid process appeared to be localized to the skin. Further, the cases were not all clinically acceptable examples of skin sarcoidosis, for this group included a sebaceous cyst, a naevus, and in three cases abrasions following accidents. Nevertheless the histological appearance was that of sarcoid tissue rather than a foreign-body giant-cell reaction. Microscopy never revealed doubly refractile crystals or other evidence of foreign particles in the skin. To distinguish them from the generalized disorder, these lesions have been termed local sarcoid-tissue reactions. The natural history and fate of these skin lesions was artificially terminated by surgical excision or plastic repair in six instances, and in the remainder clearing occurred spontaneously, but slowly, in the course of three years.

### *Relationship of Cutaneous to Generalized Involvement*

*The age at onset* (Table III and Fig. 1) can be but approximate, for undetected disease may have occurred several years earlier. The peak incidence of skin

involvement is in the fifth decade, with a mean age at onset of 42 years (range 13 to 66 years). This is an older age group than that of patients with erythema nodosum or without any cutaneous abnormality, whose mean ages at onset were respectively 32 (range 18 to 51) and 34 (range 18 to 63) years. Apart from erythema nodosum, there was no significant difference in the age at onset between the different types of skin lesion.

TABLE III

*Age and Sex Distribution*

| *Group* | *Number of patients* | *Age at onset (years)* | | *Women* | |
|---|---|---|---|---|---|
| | | *Range* | *Mean* | *Number* | *%* |
| Skin | 33 | 13–66 | 42 | 26 | 80 |
| Erythema nodosum | 62 | 18–51 | 32 | 43 | 70 |
| Non-skin | 105 | 18–63 | 34 | 45 | 43 |
| Total | 200 | 13–66 | 35 | 114 | 57 |

*Sex incidence* (Table III). Sarcoidosis affects both sexes to about the same extent, but in patients with skin lesions or erythema nodosum there was a conspicuous preponderance of women.

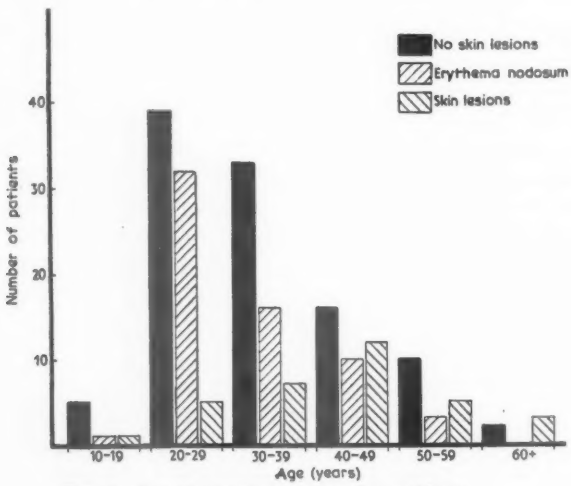


FIG. 1. Age at apparent onset of sarcoidosis.

*Intrathoracic involvement* (Table IV) occurred in 29 of 33 patients with skin lesions, and in all but three of those with erythema nodosum. The changes ranged from bilateral hilar lymphadenopathy to diffuse pulmonary mottling without enlargement of the hilar glands. Patients with lupus pernio or with persistent plaques had more advanced intrathoracic changes than those with transient maculo-papular eruptions or erythema nodosum. This difference was also reflected in the incidence of radiological clearing, which occurred in only one of the 19 patients with lupus pernio or persistent plaques, compared with five of the eight with transient maculo-papular eruptions. In the group with

erythema nodosum hilar adenopathy was bilateral and symmetrical, whereas enlargement of paratracheal nodes, which was also present in 15 cases, was unilateral and right-sided. The glandular enlargement persisted in 49 patients for from two to 12 months, with an average of six months. In seven of these patients transient diffuse mottling developed in both lungs as the hilar nodes subsided; it persisted for two to three months in six patients, and for 12 months in another. In the remaining patients the follow-up period has been too short to assess duration.

TABLE IV

*Intrathoracic Changes*

| | *Number of patients* | *Clear radiograph* | *Bilateral hilar lymph-adenopathy* | *Hilar lymph-adenopathy + pulmonary mottling* | *Diffuse pulmonary mottling* | *Subsequent complete clearing* |
|---|---|---|---|---|---|---|
| Lupus pernio | 9 | 1 | 3 | 3 | 2 | 1 |
| Persistent plaques | 10 | 2 | 1 | 3 | 4 | 0 |
| Maculo-papular eruptions | 8 | 1 | 2 | 4 | 1 | 5 |
| Skin scars | 6 | .. | .. | 5 | 1 | 1 |
| Total skin lesions | 33 | 4 | 6 | 15 | 8 | 7 (24%) |
| Erythema nodosum | 62 | 3 | 59 | .. | .. | 49 (83%) |

*Ocular sarcoidosis* (Table V) occurred more frequently in the group with skin lesions (42 per cent.), and less frequently in those with erythema nodosum (18 per cent.), than in the non-skin group (24 per cent.).

TABLE V

*Involvement of Other Tissues in Sarcoidosis With and Without Skin Involvement*

| | | *Other tissues involved* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *Lungs* | | *Eyes* | | *Lymph-nodes* | | *Spleen* | | *Bone* | |
| *Group* | *Number of patients* | *Number* | *%* | *Number* | *%* | *Number* | *%* | *Number* | *%* | *Number* | *%* |
| Skin lesions | 33 | 29 | 88 | 14 | 42 | 18 | 54 | 6 | 18 | 10 | 30 |
| Erythema nodosum | 62 | 59 | 95 | 11 | 18 | 23 | 37 | 3 | 5 | 0 | 0 |
| Non-skin group | 105 | 93 | 88 | 25 | 24 | 34 | 32 | 18 | 17 | 1 | 6 |
| Total | 200 | 181 | 91 | 50 | 25 | 75 | 37 | 27 | 13 | 11 | 5 |

*Lymphadenopathy* (Table V), other than hilar, was present at some stage of the disease in 54 per cent. of patients with skin lesions, and in 37 per cent. of the group with erythema nodosum, compared with 32 per cent. of the group without skin lesions and 37 per cent. of the whole series. *Splenomegaly* occurred with equal frequency irrespective of whether skin lesions were present, except that it was less often observed in patients with erythema nodosum.

*Bone cysts* (Tables V and VI) in hands and feet were commonest in patients with lupus pernio. They were observed in 10 of the 33 patients with skin lesions, and in 11 of the 200 patients.

*Serum-globulin abnormalities* (Table VII) were observed in one-quarter of the patients, whether they had skin lesions, erythema nodosum, or no cutaneous abnormality. They were not observed in patients with local sarcoid-tissue reactions.

### *Skin Tests*

*Mantoux tests* (Table VIII) were more often negative in patients with skin lesions than in those with erythema nodosum or in the non-skin group. In positive reactors tests were negative at high dilutions, and 100 tuberculin units were necessary to elicit a positive response. Some patients with negative Mantoux reactions revealed sensitivity to depot tuberculin (Table IX).

TABLE VI

*Involvement of Other Tissues in Cutaneous Sarcoidosis*

| *Type of skin lesion* | *Number of patients* | *Other tissues involved* | | | | |
|---|---|---|---|---|---|---|
| | | *Lungs* | *Eyes* | *Lymph-nodes* | *Spleen* | *Bone* |
| Lupus pernio | 9 | 8 | 5 | 2 | 0 | 6 |
| Persistent plaques | 10 | 8 | 1 | 8 | 3 | 1 |
| Maculo-papular | 8 | 7 | 5 | 6 | 3 | 1 |
| Scars | 6 | 6 | 3 | 2 | 0 | 2 |

TABLE VII

*Serum-Globulin Estimations*

| *Type of lesion* | *Number of patients* | *Globulin abnormalities** | % |
|---|---|---|---|
| Lupus pernio | 6 | 1 | .. |
| Plaques | 5 | 2 | .. |
| Maculo-papular | 8 | 1 | .. |
| Scars | 6 | 3 | .. |
| Total skin group | 25 | 7 | 28 |
| Erythema nodosum | 50 | 12 | 24 |
| Non-skin group | 73 | 21 | 28 |
| Total series | 148 | 40 | 27 |
| Sarcoid reactions | 5 | 0 | .. |

* Serum-globulin level above 3·5 g. per 100 ml., or electrophoretic pattern showing relative preponderance of $\alpha$-, $\beta$-, or $\gamma$-globulin.

TABLE VIII

*Results of Mantoux Tests*

| *Group* | *Number of patients* | *Mantoux test (100 tuberculin units)* | | | |
|---|---|---|---|---|---|
| | | *Positive* | | *Negative* | |
| | | *Number* | % | *Number* | % |
| Skin lesions | 33 | 7 | 21 | 26 | 79 |
| Erythema nodosum | 62 | 33 | 53 | 29 | 47 |
| Non-skin group | 105 | 40 | 38 | 65 | 62 |
| Total | 200 | 80 | 40 | 120 | 60 |

*Kveim tests* (Table X) provided histological proof of sarcoid tissue in 129 of 149 patients; they were positive in 12 of 13 patients with various skin lesions, and in 53 of 57 patients with erythema nodosum. The Kveim test proved most helpful in distinguishing the form of erythema nodosum due to sarcoidosis.

*Beryllium patch tests*, using one per cent. beryllium nitrate, were negative in

30 patients distributed in the skin and non-skin groups. No reaction was observed during 48 hours, and the site was not palpable at the end of one month.

### *Treatment*

In an ill-defined condition of unknown cause it is not surprising that many forms of treatment have been given a trial. In the 33 patients with skin lesions other than erythema nodosum these treatments have included nitrogen mustard

TABLE IX

*Results of Depot Tuberculin Tests Performed on Patients with Negative Mantoux Tests*

| | | *Depot tuberculin (5 t.u.)* | | | |
|---|---|---|---|---|---|
| | | *Positive* | | *Negative* | |
| *Group* | *Number of patients* | *Number* | *%* | *Number* | *%* |
| Skin lesions | 12 | 7 | 58 | 5 | 42 |
| Erythema nodosum | 16 | 14 | 87 | 2 | 13 |
| Non-skin group | 25 | 19 | 76 | 6 | 24 |
| Total | 53 | 40 | 75 | 13 | 25 |

TABLE X

*Results of Kveim Test*

| | | *Kveim test (0·2 ml.)* | | | |
|---|---|---|---|---|---|
| | | *Positive* | | *Negative* | |
| *Group* | *Number of patients* | *Number* | *%* | *Number* | *%* |
| Skin lesions | 13 | 12 | 92 | 1 | 8 |
| Erythema nodosum | 57 | 53 | 93 | 4 | 7 |
| Non-skin group | 79 | 64 | 81 | 15 | 19 |
| Total | 149 | 129 | 86 | 20 | 14 |

(one case), calciferol (three), radiotherapy (five), antituberculous chemotherapy (six), and corticosteroid therapy (14 cases). There was no appreciable response to any treatment other than corticosteroids. Biopsies from skin and nasal lesions in six patients, before and after a substantial course of antituberculous drugs, showed no evidence of healing of the granulomata. By contrast, serial skin biopsies in six patients after treatment with oral cortisone for one month revealed a profound histological change. Well-defined sarcoid follicles composed of epithelioid cells had been replaced by a mild non-specific inflammatory cell infiltration, and in two instances the dermis appeared normal. Fourteen patients have received oral cortisone or prednisolone, and in six of these topical hydrocortisone or fluorohydrocortisone ointment was also prescribed. All have shown clinical benefit, and this has been more striking and sustained after systemic than local administration. Daily oral dosage of 100 mg. cortisone or 20 mg. prednisolone was sufficient to produce some improvement within a week in all instances. Lupus pernio became less obvious, and three female

patients were gratified to find that they no longer needed a heavy camouflage of cosmetics. Patients with lupus pernio also noted that breathing was no longer impeded by nasal crusts, which is a common accompaniment. Persistent plaques and scars became less livid, and within one month plaques were impalpable. When oral treatment is discontinued, lupus pernio and plaques gradually recur, and are again fully manifest within six months. The response to topical applications alone is less obvious, and in all six instances in which hydrocortisone or fluorohydrocortisone ointment was liberally used for a substantial trial it was necessary eventually to reinforce treatment with the oral drug. The improvement which then followed served to underline the inferiority of ointments alone. In one patient, with extensive persistent plaques, some lesions were subjected to local intradermal injections of hydrocortisone, alone or in combination with hyaluronidase. Results were disappointing, and conferred no greater benefit than ointments to the skin surface.

Patients with erythema nodosum recovered without recourse to corticosteroid therapy. They remained at rest until the tender and acute skin lesions, polyarthralgia, and fever had subsided, and they were then allowed a convalescence of about twice this period of rest in bed. Patients were then allowed to return to work in spite of X-ray changes in the chest, for hilar adenopathy gradually subsided within the ensuing 12 months.

### *Discussion*

Cutaneous sarcoidosis is but one manifestation of a generalized disease, in which intrathoracic involvement is the most frequent accompaniment. This affinity is even more evident when the stage of evolution of the intrathoracic abnormality is compared with the type of skin lesion. The earliest abnormality in chest radiographs is bilateral hilar lymphadenopathy, which may regress completely without parenchymal involvement, or may be accompanied or followed by diffuse pulmonary mottling. This in turn may regress, or may progress to irreversible fibrosis. The evolution through these various stages is always in the same direction, and is characteristic of sarcoidosis. The earliest stage, hilar lymphadenopathy, is the change which commonly accompanies erythema nodosum, whereas the later stages of diffuse pulmonary mottling are associated with persistent plaques or lupus pernio. These trends are also reflected in the incidence of radiological clearing, which occurred only once in 16 patients with long-standing skin lesions, compared with the majority of those with transient eruptions. Other tissues commonly involved in the course of cutaneous sarcoidosis are lymph-nodes, eyes, bone, and spleen, in that order of frequency. There is a peculiar predilection of a system for a particular type of skin lesion. Ocular and bone involvement are frequent in lupus pernio, whereas lymphadenopathy and splenomegaly are more commonly associated with plaques and maculo-papular eruptions. From the analysis of these associations two generalizations emerge. Bone changes were found only once in the absence of skin involvement, so that routine radiography of hands and feet is of little

diagnostic value. It does not provide information not already afforded by examination of the skin. The other generalization is based upon the frequent coexistence of skin and ocular lesions. Granulomatous uveitis in the presence of skin plaques should always arouse the suspicion of sarcoidosis.

The demonstration that cutaneous involvement is but an incident of the generalized disorder is in accord with the experience of Longcope and Freiman (1952). This being so, the question inevitably arises of defining sarcoid skin lesions which are unaccompanied by evidence of the disease elsewhere. These have been termed local sarcoid-tissue reactions. The segregation is aided by the absence of radiological involvement, positive Mantoux reactions, negative Kveim tests, and normal serum-globulin levels. In the present series the Kveim test was negative in all six patients of this group in whom it was performed, whereas it was positive in the majority of patients with the generalized disease. The occurrence of sarcoid tissue as a reaction to neoplasms, reticuloses, infections, chemicals, and trauma is well recognized (Nickerson, 1937; Gherardi, 1950; Symmers, 1951; Refvem, 1954; Lofgren, Snellman, and Nordenstam, 1955). More recently Gorton and Linell (1957) have reported local sarcoid-tissue reactions in the regional lymph-nodes of 7·9 per cent. of a series of patients with carcinomas, principally of the uterine cervix. They emphasized the distinction between these local reactions and generalized sarcoidosis on the basis of clinical, radiological, and biochemical investigations. Unless the distinction is appreciated, many local sarcoid-tissue reactions of skin, bronchus, lymph-node, muscle, or other tissue may masquerade as examples of the generalized disease. Such confusion is not restricted to diagnosis, but may extend to false claims of the aetiology and natural history of the disease, and even to misinterpretation of immunological data. In view of this distinction between the generalized and local disorder, the minimum criteria for the diagnosis of sarcoidosis are twofold. There should be suggestive clinical or radiological features, or both, with evidence of generalized involvement; and there should also be histological proof of sarcoid tissue from at least one involved tissue. Evidence of one without the other is insufficient, for clinical or radiological manifestations alone are too wide a diagnostic finding, and isolated histological evidence could be construed as a local sarcoid-tissue reaction.

The indications for corticosteroid therapy in sarcoidosis have been outlined elsewhere (James, 1956). Unlike ocular and pulmonary sarcoidosis, there is no absolute indication for treating skin lesions, since no disabling sequelae are anticipated. Patients with disfiguring lupus pernio, however, are gratified by the response to treatment. On the other hand, recurrence is likely to follow cessation of treatment. Skin lesions which are not unsightly, and which are not accompanied by ophthalmic or pulmonary lesions, do not warrant the transient benefits of treatment. When treatment is necessary systemic administration should reinforce topical applications, for this ensures that lesions other than those in the skin are also treated. Oral prednisolone or triamcinolone treatment should be continued for three months, and then gradually reduced and discontinued so as to observe whether remission has been achieved. Erythema

nodosum is not an indication for steroid therapy, because recovery is complete without it. It is often tempting to prescribe it for symptomatic relief in patients with hectic fever and severe polyarthralgia. Nevertheless it is possible that steroids interfere with some important immune mechanisms of which we are at present ignorant. It seems unnecessary to prescribe such potent drugs for such a benign and self-limiting condition.

I am grateful to Dr. H. L. Marriott and Professor A. Kekwick for their support and advice, and to other clinicians who have referred patients. I am indebted to Dr. A. D. Thomson, Bland-Sutton Institute of Pathology, for histological interpretations; to Dr. E. Knudsen and colleagues of the Courtauld Institute of Biochemistry for biochemical investigations; to Dr. J. Pepys for a supply of depot tuberculin; and to Mr. M. Turney of the Photographic Department, Middlesex Hospital. The work was undertaken during the tenure of a Leverhulme Scholarship; it formed the basis of an essay awarded the Chesterfield Medal by the Institute of Dermatology, University of London.

*Summary*

1. A series of 200 patients, with clinical and histological evidence of sarcoidosis, includes 33 patients with various skin lesions and 62 with erythema nodosum. Eruptions may be persistent or transient. Lupus pernio (nine cases) and plaques (ten cases) persisted, whereas maculo-papular lesions (eight cases) and erythema nodosum were transient. In six instances skin scars drew attention to and provided histological evidence of the disease.

2. Involvement of other tissues is correlated with that of skin, and the pattern is compared with that found in a group of 105 patients without cutaneous involvement. Cutaneous sarcoidosis is but one manifestation of a generalized disease, in which intrathoracic involvement is the most frequent accompaniment. The age of the skin lesions correlates with that of the intrathoracic abnormality. Erythema nodosum is accompanied by bilateral hilar lymphadenopathy, whereas lupus pernio and persistent plaques are associated with the later stages of diffuse pulmonary mottling. These trends are reflected in the incidence of radiological clearing, which is common with transient eruptions and rare with long-standing skin lesions.

3. Other tissues commonly involved with cutaneous sarcoidosis are lymph-nodes, eyes, bone, and spleen, in that order of frequency. Ocular and bone involvement are frequent in lupus pernio, whereas lymphadenopathy and splenomegaly are more commonly associated with plaques and maculo-papular eruptions. Bone cysts were observed only once in the absence of skin lesions, so that routine radiography of hands and feet is of little diagnostic value. Granulomatous uveitis in the presence of skin lesions should always arouse the suspicion of sarcoidosis.

4. Sarcoidosis affects both sexes equally, but there is a preponderance of women in the groups with skin lesions. Patients with cutaneous sarcoidosis

belong to an older age group than those with erythema nodosum or those without skin involvement.

5. A group of 10 patients is also described in which sarcoid tissue was present in the skin, but there was no clinical or radiological evidence of the disease elsewhere. Mantoux tests were positive, Kveim tests negative, and serum-globulin levels normal. These local sarcoid-tissue reactions must be distinguished from generalized sarcoidosis. Minimum criteria for the diagnosis of sarcoidosis comprise suggestive clinical or radiological features or both, together with histological confirmation.

6. Mantoux tests were more often negative in patients with skin lesions than in those with erythema nodosum or in the 'non-skin' group. Some patients with negative Mantoux reactions revealed sensitivity to depot tuberculin.

7. The Kveim test was positive in most patients with skin lesions. It was particularly helpful in distinguishing the form of erythema nodosum due to sarcoidosis.

8. Beryllium patch tests were uniformly negative in a sample of patients distributed in the skin and non-skin groups.

9. The response to local applications, intradermal injections, and systemic administration of corticosteroids was noted. Oral administration is preferable to topical therapy. The indications for corticosteroid therapy usually depend on accompanying lesions, and only to a lesser degree on the cutaneous process. This is an additional indication for systemic rather than local administration of the cortisone drugs. Erythema nodosum is not an indication for steroid therapy, because recovery is complete without it.

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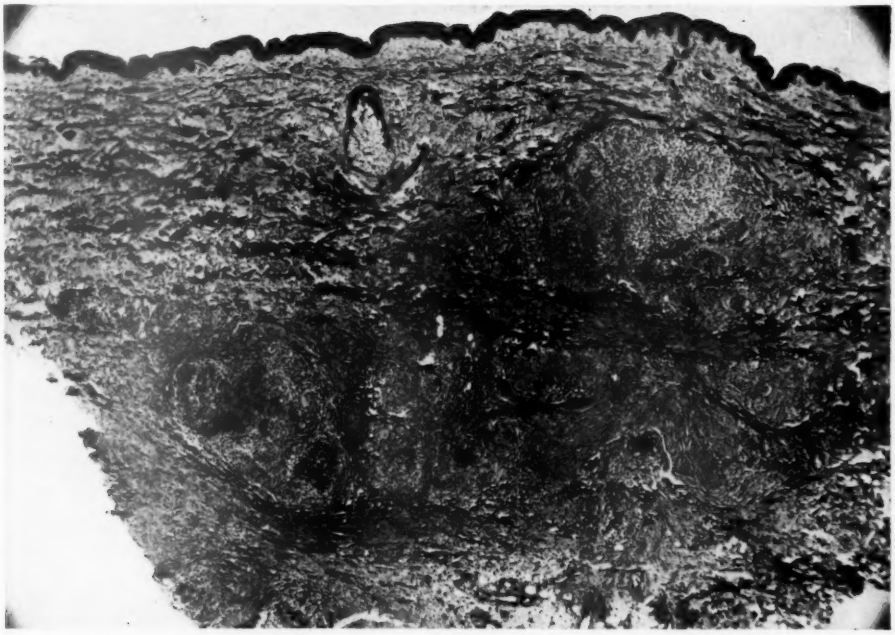
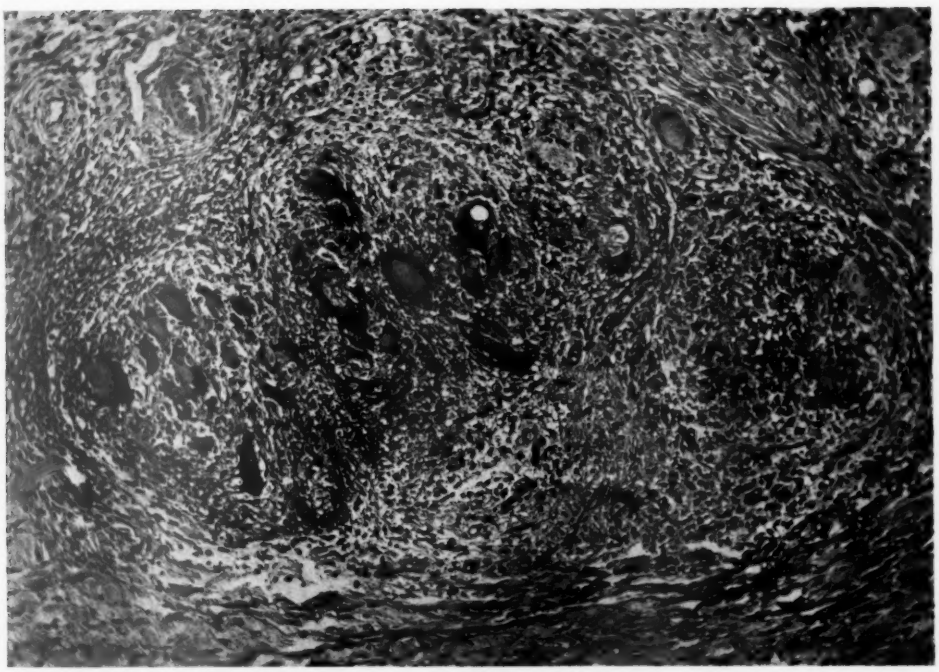


(*a*)



(*b*)

FIG. 2. Section of sarcoid tissue in dermis, showing well-defined follicles composed of pale-staining epithelioid cells, giant cells, a thin peripheral ring of lymphocytes, and inconspicuous central necrosis (haematoxylin and eosin, (*a*) ×28, (*b*) ×100)

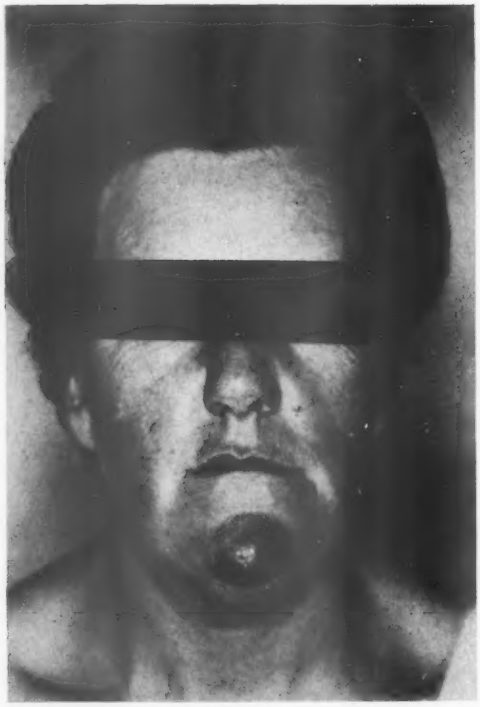


FIG. 3. Lupus pernio involving the nose, cheeks, and chin

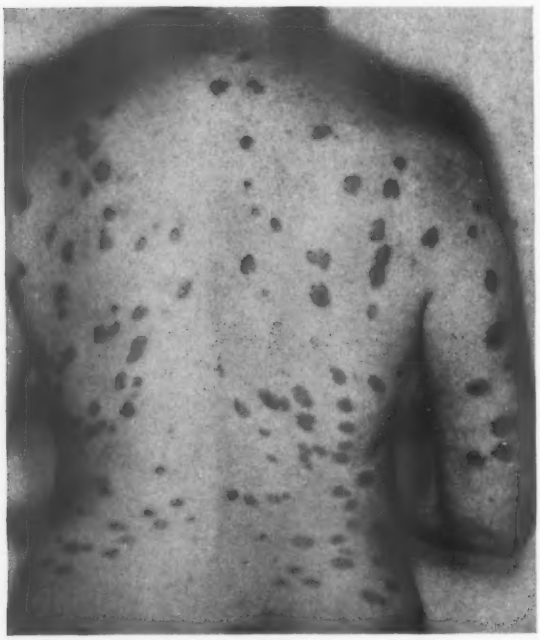


FIG. 4. Persistent plaques on the trunk

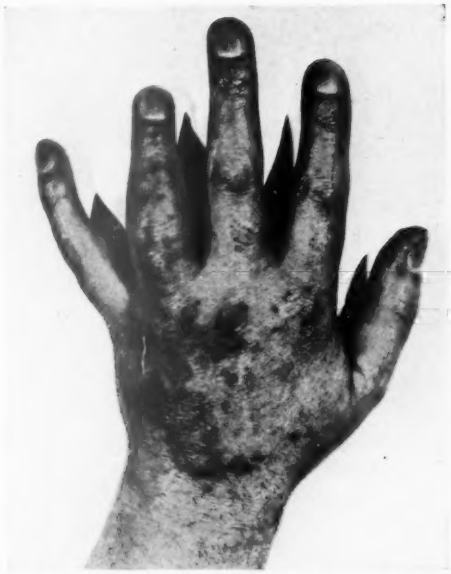


FIG. 5a. Persistent plaques on the dorsum of the left hand, with a swollen ring finger

FIG. 5b. The same patient. Bone cyst in the proximal phalanx of the swollen ring finger

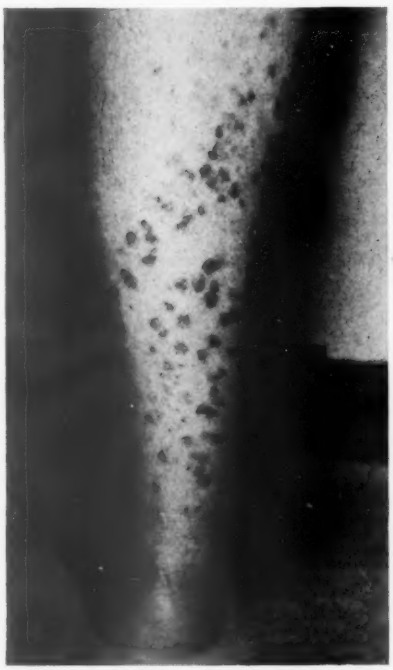


FIG. 6. Transient recurrent maculo-papular eruption on the left calf

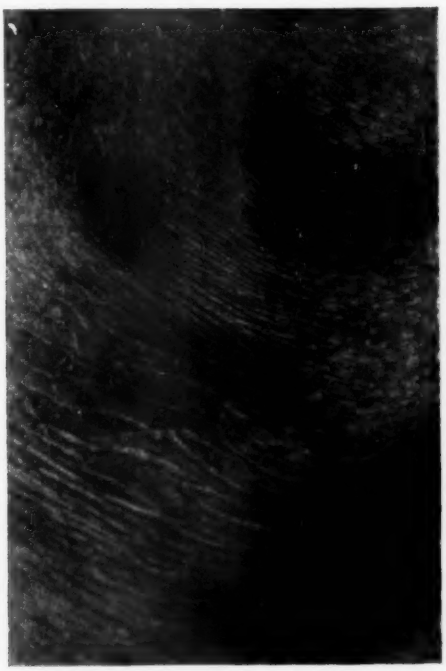


FIG. 7. Purple knee scars at the sites of old trauma

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# THE IMMEDIATE TREATMENT OF NON-EMBOLIC HEMIPLEGIC CEREBRAL INFARCTION[1]

By A. BARHAM CARTER

(From the Ashford Hospital, Middlesex)

THE diagnosis of 'cerebral thrombosis' is usually made in cases of acute hemiplegia in middle-aged or elderly patients where there is no evidence of haemorrhage or of any embolic source. For many years this diagnosis has been accepted by clinicians, but evidence is accumulating which suggests that in many such patients there has been no cerebral arterial thrombosis, although ischaemic cerebral softening has occurred, presumably associated with diminished cerebral blood-flow and degenerative vascular changes in the vessels of the head and neck. Hicks and Warren (1951) analysed 100 cases coming to autopsy and previously diagnosed as cerebral thrombosis, and found that in 60 of them, although cerebral softening and arterial degeneration were present, no occlusion of the vessel supplying the infarcted area could be found. No examination of the carotid or vertebral arteries was made. Angiographic studies made during life by Livingston, Escorbar, and Nichols (1955) confirmed this finding; they demonstrated normal cerebral arterial filling in 12 patients out of 30 with recent hemiplegia supposedly due to thrombosis. The history of these 12 patients in no way differed from the other 18, in whom occlusion by a thrombus was found. These findings have been confirmed, and are now accepted as generally applicable, so that two out of every five patients diagnosed as suffering from cerebral thrombosis have probably had no thrombosis in the cerebral vessels. A better term would be cerebral infarction, and to distinguish this condition from cerebral embolism it should be called non-embolic. The alternative 'cerebral occlusion' is better than 'cerebral thrombosis', but in many cases even occlusion cannot be demonstrated, so that for the persisting hemiplegia cerebral infarction seems the best description. The present study records the results of a therapeutic trial in four groups of such patients, the first a control series, the second treated with repeated stellate block, the third with vasodilator drugs, and the fourth with anticoagulants.

## *Current Views*

Until recently the treatment of cerebral infarction has been concerned first with preservation of life and prevention of nursing disasters, and later with rehabilitation of the disabled patient. No real attempt at influencing the occlusion or its effect on the brain was made until 1934, when Leriche and

[1] Received April 22, 1958.

Fontaine suggested that stellate ganglion block would improve the blood-supply of infarcted brain; and since then other methods have been used.

1. *Vasodilator drugs.* Many drugs with vasodilator properties have been used to increase cerebral blood-flow, but most of them appear to be ineffective. Aminophylline, nicotinic acid, and alcohol do not increase cerebral circulation in man (Wechsler, Kleiss, and Kety, 1950; Scheinberg and Jayne, 1952; Patterson, Heyman, and Nichols, 1950); papaverine is apparently capable of producing a 20 per cent. increase (Shenkin, 1950–1); sodium nitroprusside and histamine, although producing cerebral vasodilatation, have no measurable effect on the cerebral blood-flow, because they also lower systemic arterial pressure (Page, 1954; Shenkin, 1950–1). Tolazoline hydrochloride ('priscol') is a powerful vasodilator, and was thought to increase cerebral blood-flow, but Scheinberg, Blackburn, and Rich (1953), using Kety's nitrous-oxide method, did not detect any alteration in normotensive patients. Clinical evidence of its use in cerebral infarction was contradictory until Clarke, Hughes Jones, and Logothetopoulos (1954) showed clearly that intravenous tolazoline (25 mg.) had no constant effect on the cerebral blood-flow in patients with cerebrovascular disease. Smith and Turton (1951) had previously reported temporary amelioration of acute cerebral arteriosclerotic symptoms by this method of treatment. The most effective method of increasing cerebral blood-flow is the inhalation of 5 to 7 per cent. carbon dioxide; this will produce approximately a 75 per cent. increase (Kety and Schmidt, 1948). This form of treatment, however, was used as a routine for acute cerebral infarction by Altschule (1954) in Boston without improvement in his results, and Kety (1954) has suggested that 'in acute cerebral infarction nature is using all the carbon dioxide therapy possible by means of the tremendous tension of this gas which must be accumulating in these ischaemic areas'. Waltz, von Weiss, and Stevens (1957) have shown that inhalation of 7 per cent. carbon dioxide in oxygen improves the electroencephalogram in patients with acute cerebral infarction, but this improvement was not accompanied by clinical changes. From this evidence it seems that the clinical value of vasodilator drugs remains to be demonstrated.

2. *Stellate ganglion block.* It has been shown in a series of both normotensive and hypertensive patients (Scheinberg, 1950) that successful bilateral stellate block produces no change in either cerebral blood-flow or cerebral vascular resistance. Many clinical reports of its good results, however, have appeared, and Murphy (1954) suggested that there is little to lose and possibly a great deal to gain by this treatment. Amyes and Perry (1950) reported good results in 44 cases, with electroencephalographic improvement, and Naffziger and Adams (1950) obtained a '59 per cent. recovery rate' in the treatment of cerebrovascular accidents. Walsh (1956) was enthusiastic about the value of stellate block in cerebral infarction, among many other conditions, and in 198 cases of cerebral catastrophe seen in general practice found that 'approximately 50 per cent. of patients with hemiplegia following cerebral thrombosis improve after stellate block, and where improvement occurs it is so dramatic and instantaneous that it cannot be attributed only to the natural course of the disease'.

There were no control subjects to his series. Millikan (1954) stressed the importance of natural recovery, and in a small controlled series found that the patients who received stellate block for cerebral infarction fared worse than the untreated control patients, thus confirming his view (Millikan, Lundy, and Smith, 1953) that many patients who improve after stellate block would have recovered without it. Even if it could be shown that stellate block relaxes constricted vessels, this vasoconstriction may be associated with lowered intraluminal pressure, and in such cases perhaps more harm than good would result. Whether the vasoconstriction due to spasm is ever sufficient to produce permanent changes is uncertain, and a controlled series of cases is needed from which data may be collected.

3. *Corticosteroid therapy.* The third condition interfering with recovery of blood-flow after infarction is cerebral oedema. Although part of this oedema may be mechanical in origin, part of it must be produced by cellular reaction to the damaging ischaemic process. Cortisone, and recently prednisone and prednisolone, have proved themselves powerful inhibitors of cellular reaction, and it is therefore reasonable to suppose that they may effectively lessen this oedema. Russek, Russek, and Zohman (1955) reported results in 30 men and five women, suffering from recent cerebral infarction, who were treated for three weeks with cortisone in decreasing doses. There was no control group, but the authors noticed striking improvement within 24 hours in 21 patients, with amelioration of paralytic signs and beneficial changes in mental state. Whether amelioration of cerebral oedema following embolism makes any difference to the degree of permanent recovery has not been proved, and it is well to remember the potential dangers of further thrombosis as a result of cortisone therapy (Cosgriff, 1951).

4. *Anticoagulant therapy.* Medical opinion is sharply divided on the value and danger of this form of treatment after cerebral infarction. Brain (1954) suggested that the reason why anticoagulants have been little used in England in the treatment of cerebral vascular lesions is the possible risk that bleeding may occur from the infarcted area, and particularly from any infarcted vessel. Elkington (1955) likewise considered that in the brain there is a risk of haemorrhage that does not exist in cases of coronary thrombosis. In North America anticoagulant treatment is more popular. Luckey (1954) discussed its use in patients suffering from thrombotic cerebral infarction, and suggested that recanalization might occur more rapidly, and that the marginal reserve of adjacent areas of the brain might be increased. He also thought that further spread of thrombosis might be prevented in the brain, and that extracerebral thrombo-embolic episodes, such as pulmonary infarction, might be prevented. There is much evidence supporting the value of anticoagulant therapy in patients with basilar or carotid stenosis due to atherosclerosis in whom transient symptoms occur from intermittent circulatory insufficiency (Millikan, Siekert, and Shick, 1955 *a*, *b*); and Fisher (1957), in describing 10 years' experience in the treatment of cerebral infarction, agreed on the value of this treatment. There is less agreement as to the effects of anticoagulant drugs after cerebral infarction

has occurred, and Ushiro and Schaller (1957) were not convinced that they significantly alter the course of the condition. Meyer, Wegner, Kane, and Reinmuth in 1957 investigated 90 cases of occlusive disease of the basilar and carotid arteries, and evaluated the results of treatment by changes in the electroencephalogram. They found that anticoagulant therapy aided in preventing ischaemic episodes, but were not convinced that any benefit occurred in cases of infarction. Denny-Brown and Meyer in 1957 described some very interesting work on monkeys, and found that occlusion of the middle cerebral artery of the healthy monkey had to be maintained for an hour or longer to produce an infarct. If, however, the systemic blood-pressure was lowered, infarction occurred much earlier. They also found that the progress of the infarct could be prevented, and the process of infarction reversed, in the early stages, by the breathing of 100 per cent. oxygen, by raising the blood-pressure, or by restoring the blood-flow within the occluded vessel. In addition to these methods, heparin appeared to prevent further extension of ischaemic infarction, but reversed early stasis only when there was an associated rise of blood-pressure.

With regard to the dangers of anticoagulant treatment, the question of bleeding from or into the cerebral infarction is obviously of the greatest importance. Pathological work has demonstrated (Adams and Vander Eecken, 1953) that acute cerebral infarcts are at least partially haemorrhagic in approximately 65 per cent. of cases. These workers considered that the occurrence of significant haemorrhagic changes in brain infarcts is related chiefly to intermittent occlusion of arterial channels, usually due to a migrating thrombus. Sibley, Morledge, and Lapham (1957) have shown that experimental haemorrhagic cerebral infarcts in dogs may be made to bleed further by the administration of dicoumarol. When the experimental infarcts were anaemic, no such tendency was found. The authors suggested that these observations preclude the use of anticoagulant drugs in the treatment of patients who have suffered recent infarction due to embolism. This suggestion, however, was not borne out in a recent clinical report on the treatment of embolic infarction (Carter, 1957). Moyes, Millikan, Wakim, Sayre, and Whisnant (1957) showed that the infarctions produced in dogs by the injection of plastic vinyl acetate into the internal carotid were more haemorrhagic in the animals which received anticoagulants. Wright, Marple, and Beck (1954), however, showed that in their series animals receiving anticoagulants showed no increase, compared with controls, in the amount of blood around myocardial infarctions, and Wright and McDevitt in 1954 found no clinical evidence that anticoagulant treatment was harmful in haemorrhagic cerebral infarction.

### *Patients Investigated*

It was decided to record the results in all the patients below the age of 80 with non-embolic cerebral infarction and hemiplegia admitted to the Ashford Hospital, Middlesex, from 1952 to the end of 1955. These patients were all seen and treated by the author, and fall into four chronological groups. In

1952 no specific treatment was given, and the patients form a control group; in 1953 repeated stellate block was employed; in 1954 vasodilatation was effected by means of intermittent inhalation of carbon dioxide in oxygen; and in 1955 anticoagulant therapy was used. The results as to survival and degree of recovery were collected and compared in the same way as those obtained with patients suffering from cerebral embolism (Carter, 1957). The method of comparing historical groups may be in some ways unreliable (Reid, 1954), but in conditions of infrequent occurrence, where random selection is not possible, it

TABLE I

*Patients with Acute Hemiplegia admitted to Ashford Hospital, showing Sex and Aetiology*

| *Year* | *Number of patients* | *Male* | *Female* | *Thrombosis* | *Haemorrhage* | *Embolism* | *Tumour* |
|---|---|---|---|---|---|---|---|
| 1952 | 142 | 72 | 70 | 54 | 70 | 16 | 2 |
| 1953 | 157 | 77 | 80 | 62 | 74 | 18 | 3 |
| 1954 | 137 | 60 | 77 | 47 | 72 | 15 | 3 |
| 1955 | 139 | 65 | 74 | 56 | 70 | 11 | 2 |
| Total | 575 | 274 | 301 | 219 | 286 | 60 | 10 |
| Per cent. | 100 | 48 | 52 | 37 | 50 | 11 | 2 |

may have value provided that accessory methods of treatment are consistent and nursing care is uniformly adequate. These conditions were satisfied in the present series. The total figures relating to hemiplegia have been analysed in Table I; the figures in all groups are very similar, and show that haemorrhage accounted for half the total cases, embolism for a tenth, and thrombosis for over a third. American figures (Murphy, 1954) differ from these, and suggest that, of all cerebrovascular accidents, cerebral thrombosis accounts for 65 per cent., embolism for 5 per cent., and haemorrhage for 20 per cent., the remaining 10 per cent. being cases of subarachnoid haemorrhage. Possibly this difference is due to the fact that the hospital concerned with the present study accepts all local patients referred to it, and also some from the wider net of the Emergency Bed Service; these unselected admissions may reflect more accurately the natural incidence of disease. The numbers in this series do not include any patients over the age of 80, because it was thought that radical treatment might harm them. The numbers so excluded in each year were fairly uniform: 10 in 1952, 14 in 1953, 11 in 1954, and 13 in 1955.

### *Diagnosis*

The diagnosis of non-embolic hemiplegic infarction is usually made in middle-aged or elderly patients suffering from persistent hemiplegia, without any obvious embolic source, in whom the diagnosis of cerebral haemorrhage is unlikely. This is of course the most important condition to rule out, especially when considering anticoagulant therapy. The patient with non-haemorrhagic stroke often has prodromal symptoms, such as paraesthesiae and transient

weakness in a limb or limbs, which may remit from time to time. The episode is likely to occur at rest or at night; the onset may be relatively slow, and the area involved may tend to increase by degrees rather than suddenly. Many patients retain consciousness, and headache is not usually a serious complaint. Unconsciousness, if present, rarely lasts more than 12 to 24 hours, vomiting is uncommon, and the blood-pressure often low. Convulsions were present in 7 per cent. of this series, and in all cases the cerebrospinal fluid was clear. These findings are of course not universal, and many exceptions occur. Glynn (1956),

TABLE II

*Patients with Non-Embolic Cerebral Infarction*

| *Year* | *Number of patients* | *Male* | *Female* | *Average age (years)* | *Right hemiplegia* | *Left hemiplegia* |
|---|---|---|---|---|---|---|
| 1952 | 54 | 24 | 30 | 62 | 22 | 32 |
| 1953 | 62 | 30 | 32 | 65 | 29 | 33 |
| 1954 | 47 | 23 | 24 | 64 | 21 | 26 |
| 1955 | 56 | 27 | 29 | 65 | 27 | 29 |
| Total | 219 | 104 | 115 | 64 | 99 | 120 |
| Per cent. | 100 | 48 | 52 | .. | 45 | 55 |

reporting a series of 315 cases of vascular diseases of the nervous system, found 164 diagnosed as cerebral thrombosis; and of these patients 58 per cent. showed a sudden onset, reaching a climax within a few minutes, 69 per cent. had a diastolic blood-pressure of over 100, and 22 per cent. lost consciousness initially. None had blood in the cerebrospinal fluid, and this seems the most constantly correct finding among the accepted diagnostic criteria of thrombosis, although it does not exclude a contained intracerebral haemorrhage. The total number of patients with 'cerebral thrombosis' in the present series is analysed in Table II. There are 219 in all, out of a total of 267 including patients over the age of 80. It is evident that the numbers, sex incidence, and average age are reasonably consistent in the four groups. The sexes were about equally involved (most authorities suggest that thrombosis is twice as common in men (Murphy, 1954)), and left hemiplegia was commoner than right in the ratio of 11 to 9.

### *Methods of Treatment*

In 1953 unilateral stellate ganglion block was performed through the anterior approach in all cases, and repeated daily for 10 days. Between 5 and 10 ml. of 1 per cent. xylocaine were injected on the side opposite to the hemiplegia, and a positive Horner's sign was considered necessary to establish success. Approximately 85 per cent. of the injections produced this sign, and any return of power was noted. Only the crudest tests of power were employed—the ability to raise the straight arm forward, and the length of time this position could be maintained.

In 1954 an attempt was made to increase cerebral blood-flow by means of vasodilatation. Papaverine, tolazoline hydrochloride (priscol), and other vasodilator drugs were considered, but in view of the age of many of the patients

their use was thought to be not without danger to the coronary vessels. Moreover, it had already been shown (Kety and Schmidt, 1948) that their effect was trivial compared with that of the inhalation of a mixture of 5 per cent. carbon dioxide in oxygen, which has the added advantage of not lowering the systemic blood-pressure. This mixture was given for five minutes every hour through a B.L.B. mask for the first 48 hours of hospital treatment.

In 1955 anticoagulant drugs were used in the following way. Once the diagnosis of cerebral infarction had been made, and the possibility of cerebral haemorrhage excluded on clinical grounds and by the results of lumbar puncture, 12,500 units of heparin were given intravenously, followed by two similar doses intramuscularly at six-hourly intervals; with the first dose of heparin oral anticoagulant therapy was begun, and was continued for 14 days in all cases. This time was chosen because it has proved the most valuable to the author in cases of venous thrombo-embolism. Phenylindanedione was used, as it takes effect in about 18 hours, so that a continuous anticoagulant effect was maintained from the beginning by combining it with heparin. Biscoumacetate ('tromexan') has very much the same action, but is more expensive, and the drugs with more prolonged action, such as dicoumarol, were considered less suitable, as their effects are slower in onset and continue long after treatment has stopped. The dosage of phenylindanedione was 300 mg. in divided doses for the first 24 hours, 200 mg. for the next 24 hours, and then usually between 100 and 150 mg. daily according to the prothrombin time. The prothrombin level remained between 10 per cent. and 30 per cent. of normal. In patients over the age of 65 this dosage was modified in view of the difficulty of control of the prothrombin time in a few patients over this age who were treated by anticoagulants for cerebral embolism (Carter, 1957). Two-thirds of the dose used for patients below the age of 65 was given, so that the prothrombin time was kept between 25 and 35 seconds. Similar precautions were taken with hypertensive patients, so that those with a systolic pressure over 180 or diastolic pressure over 110 were given the smaller dosage. It was found that for the younger non-hypertensive patient the desired prothrombin level of between 10 per cent. and 30 per cent. was equivalent to a prothrombin time of from 48 to 36 seconds, so that the aim was to keep the prothrombin time in this type of patient between three and four times the normal, and in the more elderly or hypertensive patient between two and three times the normal.

### *Results*

*Assessment.* The patients were followed up for a year, and an assessment was then made by clinical examination. They were divided into four groups: 'recovered', 'improved', 'not improved', and 'died'. Recovery meant that the patient noticed slight or no disability, and was able to return to a normal life with full work. Some loss of fine-movement dexterity in the hand was considered compatible with 'recovery' if the above criteria were fulfilled. Probably all patients with initial complete hemiplegia continue to show permanent slight

pyramidal signs. 'Improved' meant that some useful movement was possible at the elbow and wrist. 'Not improved' indicated the group in which no return of arm movement occurred below the shoulder, although some leg function was regained. Almost all patients surviving hemiplegic cerebral infarction regain some movement of the shoulder and of the lower limb.

### *Analysis of Results*

The results are shown in detail in Table III, and it is clear that the difference in the group results is not very significant. If the 'recovered' and 'improved' groups are added together, and the 'not improved' and 'died' similarly treated, it will be seen in Table IV that there is no difference in outcome between the

TABLE III

*Results of Treatment*

| *Year* | *Number of patients* | *Recovered* | *Improved* | *Not improved* | *Died* | *Treatment* |
|---|---|---|---|---|---|---|
| 1952 | 54 | 13 | 12 | 9 | 20 | Control group |
| 1953 | 62 | 14 | 16 | 8 | 24 | Stellate block |
| 1954 | 47 | 15 | 12 | 4 | 16 | Cerebral vasodilatation ($CO_2$ inhalation) |
| 1955 | 56 | 18 | 15 | 8 | 15 | Anticoagulants |
| Total | 219 | 60 | 55 | 29 | 75 | .. |
| Per cent. | 100 | 28 | 25 | 13 | 34 | .. |

TABLE IV

*Comparison of Results*

| *Year* | *Treatment* | *Patients who recovered or who were improved* | *Patients who died or did not improve* |
|---|---|---|---|
| 1952 | Control group . . . | 25 | 29 |
| 1953 | Stellate block . . . | 30 | 32 |
| 1954 | Cerebral vasodilatation . . | 27 | 20 |
| 1955 | Anticoagulants . . . | 33 | 23 |

patients in the control series and those who were treated by stellate ganglion block. In each of these groups the patients who died or did not improve outnumbered those showing any recovery. In the case of patients treated by repeated inhalation of $CO_2$ this trend is reversed, so that more patients recovered than not, and in the anticoagulant series this difference is more marked, 60 per cent. (33 out of 56) of the patients showing some recovery. Not even the most optimistic physician would think these figures significant, but they were of sufficient interest to justify further analysis.

It soon became apparent that the usual prognostic factors, such as age, severity and extent of the lesion, presence of unconsciousness, delay in admission resulting in dehydration and bed sores, previous 'strokes', and the presence of other diseases, were equally distributed throughout the four groups, and were not associated with the slightly improved figures for the patients treated during 1954 and 1955. In all groups the patient most likely to die was the neglected old man in poor condition with the signs of long-standing ischaemic heart

disease, in whom specific treatment of any kind was unavailing. When, however, a study was made of the time taken for the stroke to develop, some interesting facts came to light. This study showed that there were three types of onset

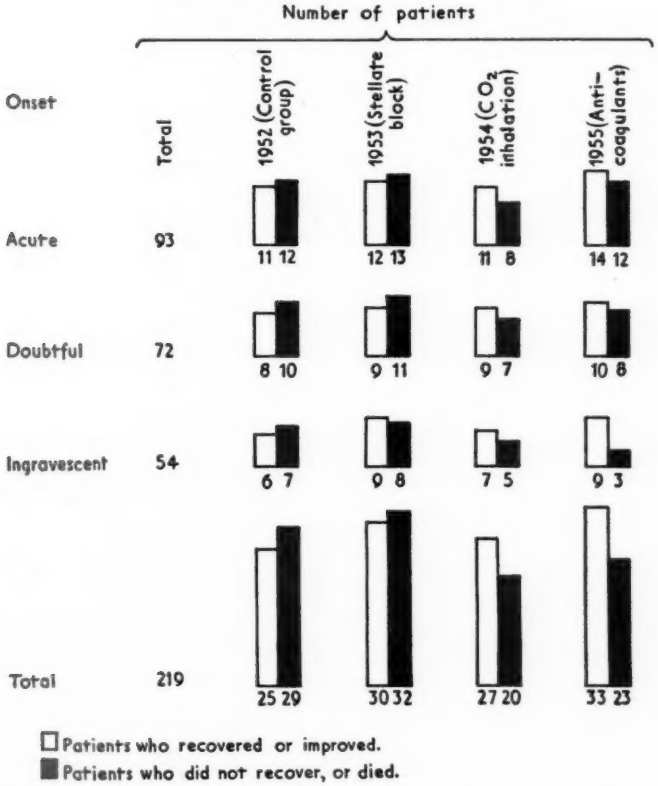
TABLE V

*Time for Full Development of Stroke*

| | *Number of patients* | | | | |
|---|---|---|---|---|---|
| | *Total* | *1952* | *1953* | *1954* | *1955* |
| Acute (0 to 6 hours) . . . . | 93 | 23 | 25 | 19 | 26 |
| Doubtful (found with stroke complete) . | 72 | 18 | 20 | 16 | 18 |
| Ingravescent (over 6 hours) . . . | 54 | 13 | 17 | 12 | 12 |
| Total . . . . . | 219 | 54 | 62 | 47 | 56 |

TABLE VI

*Relation of Prognosis to Onset and Treatment*




(Table V). The first was almost immediate, the stroke reaching its maximum effect at once or within a few hours. In the second type the interval between onset and completion of the stroke was doubtful, because the patient was found

unconscious or with a complete hemiplegia, and the only information available was that he had been well some hours previously. The third type of onset was slower, with an interval of six hours or more, and the stroke often did not develop to complete hemiplegia. It was found that these three types were fairly equally distributed over the four years' survey, and in almost exactly one-third of the patients the type of onset could not be accurately determined. In one-quarter of the patients the onset was ingravescent, and in the others (42 per cent.) the stroke had reached its maximum effect quickly. In a few cases of the

TABLE VII

*Results of Treatment in Patients with Stroke of Slow Onset*

| | | *Number of patients* | | | | |
|---|---|---|---|---|---|---|
| *Year* | *Treatment* | *Total* | *Recovered* | *Improved* | *Not improved* | *Died* |
| 1952 | Control . . . | 13 | 3 | 3 | 4 | 3 |
| 1953 | Stellate block . . | 17 | 4 | 5 | 4 | 4 |
| 1954 | $CO_2$ inhalation . . | 12 | 4 | 3 | 2 | 3 |
| 1955 | Anticoagulants . . | 12 | 7 | 2 | 2 | 1 |

ingravescent type (six patients) an apparently delayed acute extension of the lesion became noticeable later. These figures may suggest that, apart from clinical cerebral embolism, embolic vascular disease plays more part in cerebral infarction than has been thought, particularly since even in proved cases it is often difficult to find the embolic material in the vessel supplying the infarcted area.

Any attempt to correlate prognosis with acuteness of onset appeared at first to be of very doubtful value, because the type of onset was uncertain in so many cases that any statistical analysis would fail. There was, however, a trend to greater improvement in results in the 1954 and 1955 groups, more patients recovering than not in the overall picture (60 to 43), compared with the opposite tendency in 1952 and 1953 (55 to 61) (Table VI). In one group this trend was so marked as to be significant, and this group was that of patients with an ingravescent stroke treated with anticoagulants. Details of the results, in all years, in patients with this type of onset are given in Table VII. Here it is seen that the 50 per cent. improvement (22 out of 42), which is steady in the first three years, becomes 75 per cent. (nine out of 12) in the year of anticoagulant treatment. This tendency is to be expected if the view is accepted that increase in symptoms and signs may be associated, if a clot is present, with its extension, or its fragmentation to produce distal embolism, or with the onset of thrombosis in those patients whose early symptoms are due to cerebral insufficiency without actual clotting.

### *Analysis of Pathological Material*

Evidence has already been presented suggesting that two out of every five patients diagnosed as suffering from cerebral thrombosis have no discernible clot in the cerebral vessels, and the cause of infarction in these cases has been

considered as cerebral vascular insufficiency due to degenerative narrowing of the arteries. To this possibility has been added that of occlusion of the internal carotid artery in the neck; here the aetiology is similar, and both complete occlusion and stenosis occur much more frequently than was supposed by earlier workers. Many papers have appeared on this subject, and have been reviewed by Symonds (1957). Authorities agree that clinical diagnosis between cerebral thrombosis and cerebral vascular insufficiency severe enough to cause infarction is often impossible (Millikan, 1954). Moreover, in a study of autopsy material in an attempt to correlate the clinical picture with post-mortem findings, Fisher (1952) found that the commonest clinical presentation of internal carotid artery occlusion in the neck was that of classical middle cerebral thrombosis. The obvious diagnostic procedure to assist in accurate diagnosis of cerebral infarction is carotid arteriography, but this has its disadvantages. In the 1954 and 1955 groups arteriography was given consideration as a routine diagnostic procedure for all hemiplegias, but the risk of converting a partial weakness into a complete paralysis, coupled with the doubt whether occlusion of small vessels would be shown by this method, was considered to make its use unjustifiable. Therefore, since clinical diagnosis may be impossible, a study of post-mortem material was made in the 1954 and 1955 groups. The other groups are not included, because no examination of the carotid arteries was made in 1952 and 1953 owing to clinical unawareness of its importance. In 1954 16 patients died, and 14 came to autopsy; in 1955 15 died, and 12 were examined *post mortem*. In the 1954 series six cases showed no thrombus, five showed a thrombus in the middle cerebral artery, and three had complete carotid occlusion, one with a recent middle cerebral block which was probably embolic. In the 1955 series five cases showed no thrombus, five showed a thrombus in the middle cerebral artery, and two showed carotid occlusion. Thus the total of 26 cases is divided into 11 without any evidence of thrombosis, 10 with middle cerebral thrombosis, and five with cervical carotid occlusion. Of the 11 patients without any sign of occlusion seven had atheroma, described as severe, involving the basilar artery as well as the circle of Willis. Two had moderate atheroma, and one very slight atheroma; one was surprisingly free from atheroma, but had been hypertensive, and showed arteriolosclerotic changes in the smaller vessels. Of the seven patients with severe atheroma, two had carotid stenosis without occlusion or mural clot, and in these cases the atheroma was severe also in the basilar artery. In no case was there any dissociation between the two arterial systems with regard to the degree of atheroma present. Possibly this fact contributed to the patients' death.

An attempt was made to correlate the type of lesion, found at autopsy to be responsible for infarction, with the rapidity of onset of symptoms. The attempt was not very satisfactory because of the number of patients 'found unconscious', nor in fact was a significant correlation found. Of the eight patients in whom the onset was acute, three had middle cerebral thrombosis, one carotid occlusion with distal embolism, and four atheroma only. Of the 14 patients with doubtful onset seven had middle cerebral thrombosis, and seven had atheroma, carotid

stenosis being present in one of the latter. Of the four ingravescent cases, carotid occlusion was present in three, and carotid stenosis without occlusion in one; this tiny group seems the most informative, because it suggests that a slow onset may go with carotid narrowing. A final point must be mentioned regarding this series. There was no difference, in the extent or nature of the infarction of the brain, between cases with and cases without organic obstruction.

### *Conclusion*

The results of treatment of cerebral infarction have not, in the main, been very conclusive in the patients recorded here, but certain trends indicate that a particular form of treatment may be beneficial to a small group. Stellate block has seemed to make no difference to the outcome, whatever the clinical onset and course of the hemiplegia, and it is suggested that this form of treatment be abandoned in cerebral infarction. Similarly, only a slight overall improvement in results was obtained by cerebral vasodilatation with inhalation of carbon dioxide, and the difference may have been due more to improvement in nursing attention while the inhalation was being given than to the inhalation itself. The results did not seem to justify its continued use and, in addition, consideration should be given to its possible harmful narcotic effects. In the year of anticoagulant treatment the results were better, and particularly so in patients whose stroke developed slowly; in these patients the improvement was significant (Table VII). The small amount of pathological material available shows that more than one type of lesion has been found in this ingravescent type of case.

One patient (Case 18, 1954), a woman aged 58, took three days to become hemiplegic. After her death, three weeks later, severe atheroma of the whole of the carotid-basilar system was found, with no occlusion, no thrombus, and no cervical stenosis of the internal carotid arteries. The vertebral arteries were not examined. In the brain there was a wedge-shaped area of softening, surrounded by petechial haemorrhages, and extending from the wall of the lateral ventricle out to the left parietal lobe and precentral gyrus.

A woman aged 70 (Case 43, 1954), without previous history, developed an insidious spreading weakness of the right face, arm, and leg, accompanied by dysphasia. She became completely hemiplegic within 24 hours, and, although not admitting to any sensory loss, had no idea of the position of the affected side. At autopsy, one week later, there was severe atheroma with stenosis around the circle of Willis, no stenosis of the basilar artery, moderate atheroma of the right internal carotid artery, and a complete occlusion 2 cm. above the bifurcation of the left internal carotid. There was softening of the left hemisphere, affecting the temporal, frontal, and parietal lobes, coming down to Broca's area anteriorly and involving the angular gyrus posteriorly. There seemed to be greater loss of cortex in the upper than in the lower part of the hemisphere.

A man of 60 (Case 23, 1955) had a history of a number of 'little strokes' for three or four days before a severe hemiplegia occurred, and was said to have

had attacks of 'painful clumsiness' of the left hand for as long as two years. He died while receiving full anticoagulant therapy, and at autopsy there was no atheroma of any consequence, and no occlusion or stenosis of the carotid or basilar arteries, but a recent clot was present in the right middle cerebral artery, and was beginning to organize. A cavity was found involving the lentiform nucleus, the internal capsule, and the outer half of the thalamus. The pathologist was not satisfied with the clinician's diagnosis of cerebral infarction, and the histological diagnosis was an astrocytoma. This seems to be an unusual case of thrombosis spreading back from a tumour, and presumably not much influenced by anticoagulants. It is also of interest that no haemorrhagic lesion could be found in the brain.

Finally, a man aged 60 (Case 30, 1954) was admitted with the history of sudden loss of consciousness six hours before admission. When he recovered consciousness he had a complete left hemiplegia, and gave a history of four weeks' increasing headaches, both generalized and with a right frontal distribution. Apart from this he had no previous history of weakness, blurring of vision, diplopia, or paraesthesiae. The right carotid pulse was weak, and he died three days later, without recovering any use of his left side. There was no sensory loss. At autopsy the immediate cause of death was a cardiac infarct. The right carotid artery was found completely blocked by a laminated but friable clot 1 cm. above its origin. In addition, a more recent clot was found plugging the right middle cerebral artery, and softening of the basal nuclei and internal capsule was evident. The rest of the carotid-basilar system showed only moderate atheroma.

The last patient described probably had occlusion of the right internal carotid artery in the neck a few weeks before death, causing only headache. Shortly before his admission a piece of clot presumably broke away from this occlusion and lodged in the middle cerebral artery, causing his stroke. This may be a more common happening than is realized, and although in this particular patient the onset of the stroke was not ingravescent, because the original carotid occlusion did not produce cerebral insufficiency, it can well be imagined that an acute event like this hemiplegia might well have been preceded by a history more in accordance with current views on the effects of carotid occlusion. The above studies show how difficult it is to make an accurate pathological diagnosis during life in patients with this type of hemiplegia. A major lesion such as complete occlusion of an internal carotid artery can apparently produce in some patients no disability at all, in others attacks of temporary cerebral ischaemia, and in others an acute hemiplegia.

It seems that in patients who show evidence of cerebral infarction characterized by a slow onset the natural history of the illness may be materially improved by the use of anticoagulant drugs. Further, the dangers of this treatment appear less in practice than might be expected from the experimental work already mentioned, especially if strict control is kept in elderly and hypertensive patients. Only one case of visceral bleeding occurred in the present series; no patient showed clinical evidence of bleeding into the brain, nor was such evidence found in those patients who died after anticoagulant treatment. A further safeguard is the absolute rule that the cerebrospinal fluid must be

clear before this treatment is begun, because in any extensive haemorrhagic infarct the fluid will be blood-stained in varying degrees, and may even be frankly haemorrhagic. It is, however, important to be aware of the dangers of even moderate visceral bleeding when cerebral ischaemia is present, because the hypotension caused by such bleeding may produce extension of the infarcted area, with catastrophic results. Meyer and Denny-Brown (1957) showed that in monkeys collateral circulation in the brain is at first opened up by lowering of intraluminal pressure, but that when this pressure falls below the critical level of 50 mm. of mercury the whole system collapses. This suggests that a reversible ischaemic anoxia of the brain may be converted to irreversible infarction by hypotension.

The results in the present series of cases suggest that anticoagulant therapy has little effect on the outcome of acute non-embolic cerebral infarction, and in view of the possible dangers its use is perhaps not justified. In the case of patients found unconscious, with the type of onset unknown, there may be some justification for this treatment, because some may have suffered a slow onset, or have had previous small infarctions. In the case of patients with ingravescent cerebral infarction, from whatever cause, the outcome seems to be more favourable after anticoagulants have been given, and it may be in this type of lesion that anticoagulant drugs will be found to produce their best effects.

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*Summary*

1. Two hundred and nineteen patients diagnosed as having non-embolic cerebral infarction, out of a total of 575 cases of apoplexy, have been studied over a four-year period. The patients were consecutive, except for the omission of 48 patients over 80 years of age.

2. Four groups were investigated: (1) in 1952 54 patients as controls, (2) in 1953 62 patients treated by repeated stellate block, (3) in 1954 47 patients treated by inhalation of carbon dioxide, and (4) in 1955 56 patients treated with anticoagulants.

3. Current views on treatment are reviewed, and difficulties in the term 'cerebral thrombosis' are discussed, together with the growing importance of arterial occlusion in the neck.

4. The results in this series are analysed and tabulated, and show that at the end of a year (1) there was no difference between the control group (1952) and the group treated by repeated stellate block (1953); (2) there was a slight but not significant improvement in the results in the group treated with inhalation of carbon dioxide (1954), and a further small improvement with anticoagulants (1955); (3) a breakdown of the figures in the 1955 group shows a significant

improvement in patients with an ingravescent onset who were treated with anticoagulants.

5. The dangers of anticoagulant treatment are discussed. Although experimental work suggests that they are important, no case of bleeding occurred in the present series. A modified course is suggested for elderly and hypertensive patients, so that the prothrombin time is kept between two and three times the normal.

6. It is suggested that anticoagulant treatment may be the method of choice in ingravescent cerebral infarction.

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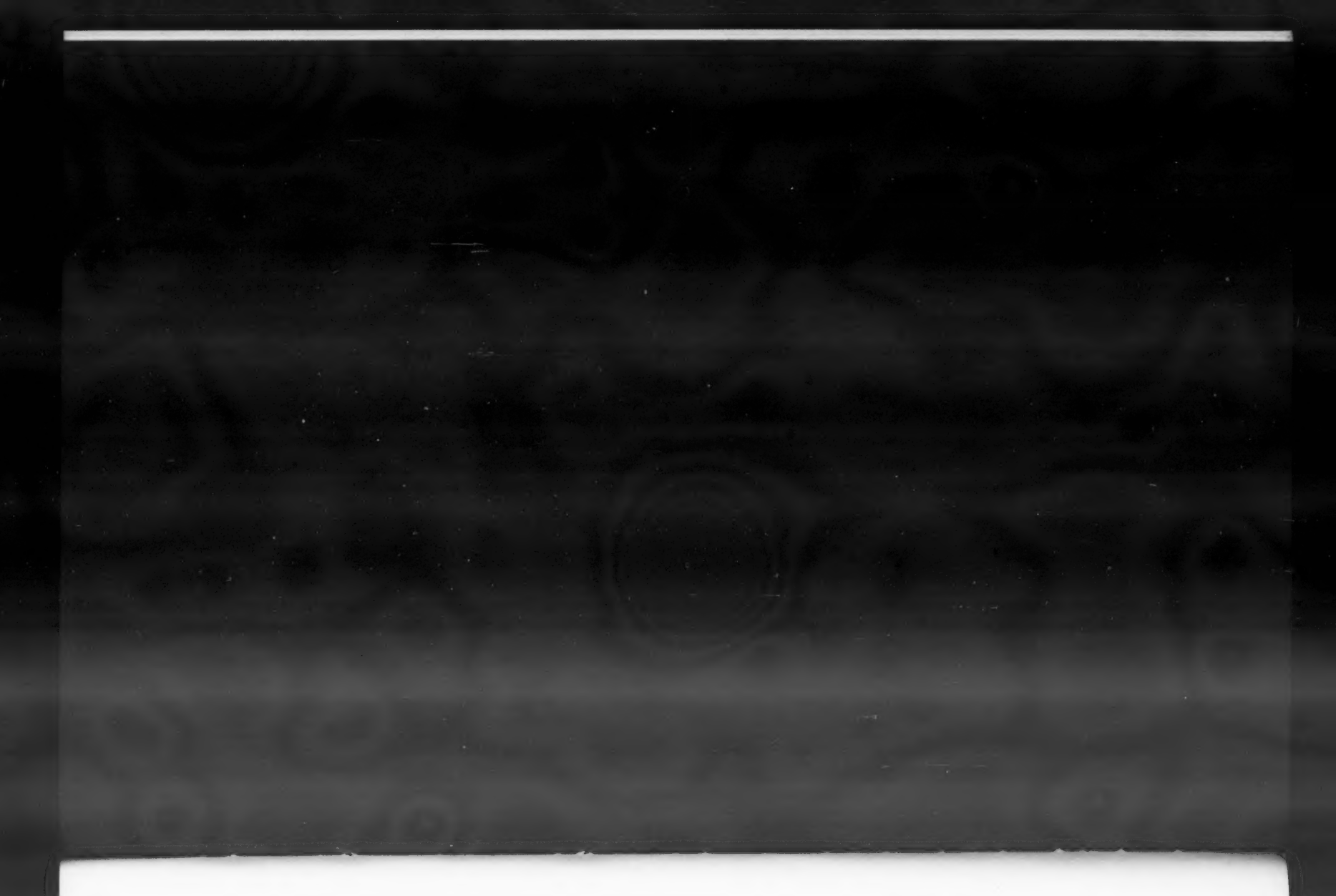

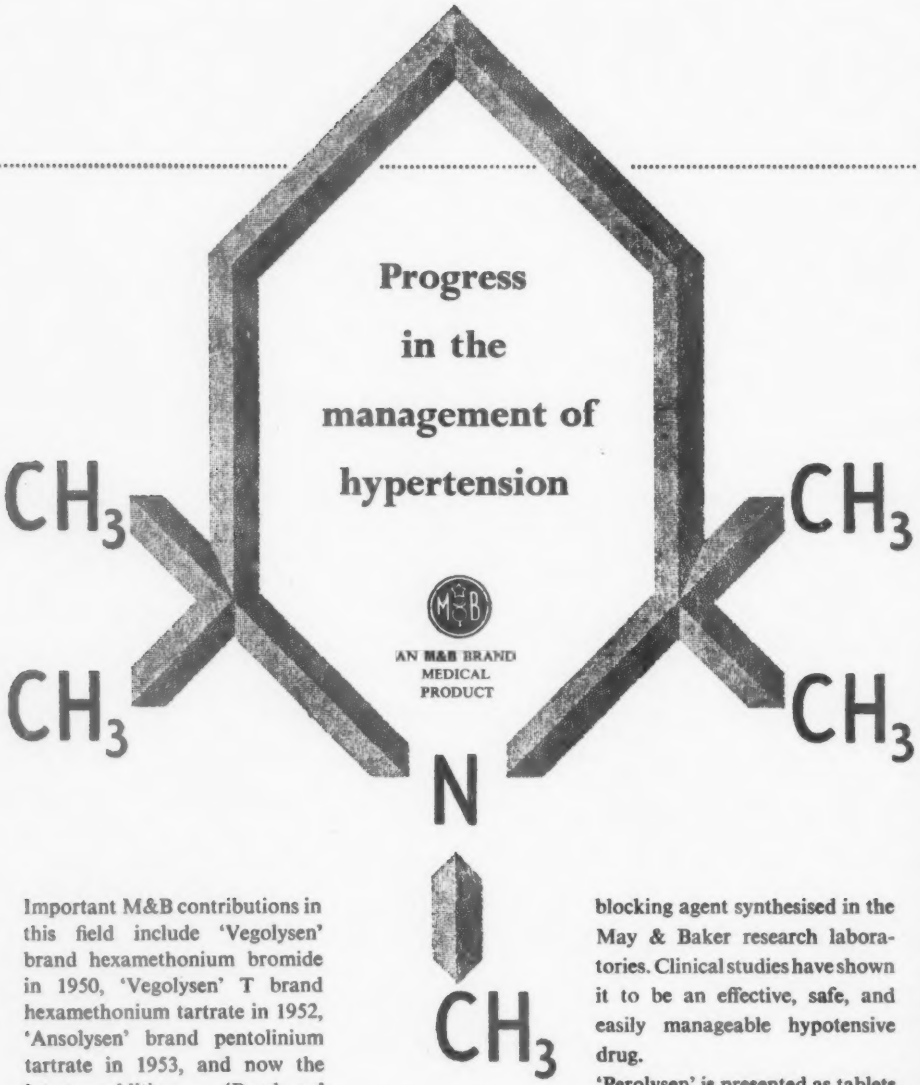


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